FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS (CTP)

TOBACCO PRODUCTS SCIENTIFIC ADIVSORY COMMITTEE

(TPSAC)

THURSDAY, OCTOBER 7, 2010

8:30 a.m. to 5:00 p.m.

Food and Drug Administration Headquarters

White Oak Building

10903 New Hampshire Avenue

Silver Spring, Maryland

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service.

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I N D E X

I N D E X (continued)

P R O C E E D I N G S

(8:36 a.m.)

Call to Order

DR. SAMET: Good morning. If everyone could take their seats, we are going to get started. I'm Jon Samet, the chair of the Tobacco Products Scientific Advisory Committee. I need to make a few official statements and then we'll get on with our business.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members

take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, this committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Introduction of Committee Members

I was now going to attempt to do this from memory, but I think I won't. We can ask the committee members now to introduce themselves.

Dan?

DR. HECK: My name is Dan Heck, principal scientist at the Lorillard Tobacco Company. I'm here representing the scientific interests of the tobacco manufacturers.

DR. LAUTERBACH: Good morning. John Lauterbach, owner of Lauterbach & Associates, consultants in tobacco chemistry and toxicology, and I'm here representing the interests of the

small business tobacco manufacturers.

MR. HAMM: Good morning. I'm Arnold Hamm. I'm representing United States tobacco farmers.

DR. MCAFEE: Good morning. I'm Tim McAfee, a director of the Office of Smoking and Health at the Center for Disease Control.

DR. BACKINGER: Good morning. I'm Cathy Backinger, chief of the Tobacco Control Research Branch at the National Cancer Institute, and I'm representing the National Institutes of Health.

DR. DELEEUW: Good morning. My name is Karen DeLeeuw and I'm the representative of Government.

DR. CONNOLLY: Good morning. My name is Gregory Connolly from the Harvard School of Public Health.

DR. TEMPLETON-SOMERS: Karen Somers, acting DFO for the committee, FDA.

DR. CLANTON: Mark Clanton, work for the American Cancer Society and I'm here providing expertise on public health, pediatrics and also

oncology.

DR. NEZ HENDERSON: Good morning. My name is Patricia Nez Henderson. I'm with the Black Hills Center for American Indian Health.

DR. HATSUKAMI: Good morning. I'm Dorothy Hatsukami from the University of Minnesota.

DR. HENNINGFIELD: Good morning. I'm Jack Henningfield from Pinney Associates and the Johns Hopkins Medical School.

DR. HUSTEN: Hello. I'm Corinne Husten, senior medical advisor in the Center for Tobacco Products at FDA.

DR. ASHLEY: I'm David Ashley. I am director of the Office of Science at the Center for Tobacco Products at FDA.

DR. DEYTON: Good morning. Lawrence Deyton, Center for Tobacco Products. And I apologize to the committee. I will have to step out right after lunch for a meeting downtown, but I'll be back.

DR. SAMET: Thank you. And let me turn

things to Karen.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: Good morning. I would first like to remind everyone present to please silence your cell phones if you've not already done so. I'd also like to identify the FDA press contact, Tesfa Alexander.

Can you please raise your hand there? Thank you.

The Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members are special government employees or regular federal government employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 U.S.C. Section 208

and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meetings and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agencies need for particular individual services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members of this committee have been screened for potential financial conflicts of

interest of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers. Those interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves receiving and discussing presentations on the publicly available industry documents as they relate to the issue of the impact of the use of menthol in cigarettes on the public health, including such use among children, African-Americans, Hispanics and other racial and ethnic minorities.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all

standing committee members and consultants to disclose any public statements that they have made concerning the issues before the committee.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach and Mr. Arnold Hamm are participating in this meeting as nonvoting industry representatives, acting on behalf of the interests of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers respectively. Their role at this meeting is to represent these interests in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company. Dr. Lauterbach is employed by Lauterbach & Associates, LLC, and Mr. Hamm is retired.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. SAMET: Okay. I think then we'll

move on to our first presentation, which will be from Corinne.

FDA Presentation: Status of TPSAC Information Requests

DR. HUSTEN: Good morning. I just want to remind everyone of the issue before the committee. As you remember, the committee is required to produce a report on the public health impact of menthol cigarettes by next March. In general, the question before the committee is what is the impact of menthol cigarettes on public health, including such use among children, African-Americans, Hispanics and other racial and ethnic minorities, and what recommendations, if any, does the TPSAC have for FDA regarding menthol cigarettes.

The committee has made several requests to FDA to support their production of the report, so I wanted to give a brief update on where we are with the various requests. So an analysis of publicly-available tobacco industry documents was requested, and there'll be presentations on that

topic at this meeting. There's a white paper summarizing the FDA literature review that was presented as a background for this meeting, and there will be a brief presentation providing an update on what has happened with the literature review since the March 30th presentation.

We have analyses in progress in terms of secondary data analysis of existing research studies on initiation, cessation, addiction and health effects related to menthol cigarette use. There's analyses underway around menthol cigarette sales data and the modeling of menthol cigarette use on initiation and cessation.

There had been requests for tobacco industry documents at the first TPSAC meeting. Those requests were sent to industry, and they were due back in August. We have received an incomplete submission from one company and no documents were identified for five of the topics requested by the committee. So I just want to let you know what those were.

So no documents were submitted for

Question 11, which was the quantities of menthol and nicotine in the cigarette by brand and sub-brand and by year for the years 2000 to 2010; Question 12, the quantities of menthol and nicotine in cigarette smoke as determined by the Cambridge filter/ISO test method, as well as the Canadian intense smoking conditions by brand and sub-brand and by year for the years 2000 to 2010; and no documents were submitted on Question 13, the manufacturing process by which menthol is introduced into menthol cigarettes, including the source and type of menthol used, the presence or use of any menthol analogues, and the manufacturing stage at which menthol is introduced. So, for example, whether it's placed on the foil in contact with the tobacco product and introduced as a flavor to reconstituted tobacco or some other way.

No documents were submitted on Question 14, the threshold, at which the companies identifying market of product by reference to its menthol flavoring or characteristics. And no

documents were submitted on Question 15, the rationale for adding menthol to cigarettes not marketed as menthol cigarettes and the criteria for determining the amount of menthol to be added.

In order to assist the committee in preparing the report, we constituted a menthol report subcommittee, which has met once. The purpose of the subcommittee was to propose a structure for the menthol report, create drafts of the chapters, working in smaller workgroups, within the subcommittee, deliberate on and discuss a draft report, and then bring that report to the full TPSAC for discussion and deliberation.

There will be small writing workgroups of two to three special government employees who are members of the committee, drafting chapters of the report that will summarize, analyze and synthesize the relevant evidence.

Industry representatives may not participate in the writing workgroups. Industry representatives are statutorily identified as consultants to the committee, and they’re not

permitted access to trade secret or commercial confidential information. And a question had come up at the subcommittee meeting about whether the industry could just waive that, but it's not feasible to obtain consent from all owners of trade secret or commercial confidential information that might be available to the workgroup.

The implication at the subcommittee meeting was that because the industry representatives couldn't actually participate in the writing of the report, that somehow they were being excluded from participation. So I'd just like to point out that there are multiple avenues for industry participation in the report, including the participation on the subcommittee and participating in the discussion and deliberation on how the report should be organized at that first subcommittee meeting, being present at these meetings, and discussing and deliberating on the evidence as presented to the TPSAC that the workgroups will be relying on in the report.

They can provide input to the workgroups if such consultation is requested by the workgroups. They'll be able to discuss it and deliberate on draft report chapters during the open subcommittee meetings, discuss and deliberate on full draft reports that will be presented to the TPSAC. We've asked the industry representatives to write an industry perspective document, and obviously, the industry representatives will participate in the discussion and development of the recommendations and in the discussion and deliberation of a final report.

Just to remind everybody about the timeline, the report is due March 23rd of next year. The requested additional information will be presented to the committee as it becomes available over the next five months so that TPSAC can discuss and deliberate on the scientific evidence. But, obviously, the subcommittee's workgroups will have to incorporate the information as it becomes available and is discussed by the full committee. We expect that

the subcommittee will need to report back to the full TPSAC around February if the report is to be completed by March.

So any clarifying questions?

DR. SAMET: John?

DR. LAUTERBACH: Dr. Husten, as common, you have us listed as consultants. It's very common for consultants in the tobacco industry to sign nondisclosure agreements with their clients. No one from the FDA has come to me and offered me to sign a nondisclosure agreement in exchange for participation on the writing committee.

DR. HUSTEN: It would be, I think, difficult for you to represent the interests of your constituents if you could not have any conversations with them about the information that's presented. And again, the whole issue of waivers around commercial and confidential, it's a very complicated process that really isn't feasible to get from everybody who might have such interest that they would want protected.

DR. SAMET: Greg?

DR. CONNOLLY: A couple of questions. At the first meeting, we spent a fair amount of time establishing the questions for the industry, and that was then published in the Federal Register. I think just for continuity, to make sure that we are making progress and that we are adhering to what we've done in previous meetings, if we could bring that copy of the Federal Register before the committee and have it present. I didn't bring mine with me, but just for continuity, I think it's very important that we be consistent in terms of what we establish and how we build.

Second point. On Question 14, you used the term "characteristic in flavoring." It was my impression we were talking about effects, chemosensory effects. Characteristic has very specific meaning under this statute and under regulations, CFR 101.22 of the FDA. So I would urge staff to stay very close to the statute where the statute does not use the word "characterizing" for the term "menthol." It does for flavorants, and unfortunately, many flavorants that were

banned still appear on industry websites as being used in cigarettes, which I don't want to see happen with menthol. There's no characterization.

One of the submissions in the paper used the term "characterization." So I think on Question 14, I'd like to go back to the Federal Register. It is menthol effects, not flavoring and characteristics. We had a very interesting -- okay. I'm done. We had a very interesting debate over taste issues, but, really, we're breaking out three effects and they should be separate.

The third thing -- and I raised it at the subcommittee, and this is just a clarifying point -- the FDA staff did give industry a six-month delay in reporting certain provisions under Section 903. Again, I request, if this report is being done by this committee under the guidance of this committee, and this committee may just want to consider this, that we formally ask FDA for a six-month delay, and we take appropriate action with the Administration and Congress for a six-month delay.

We're looking at a very complex report, a lot of complex science. To try to achieve this by March, I think is going to be a herculean task. If there is already a precedent to giving the tobacco industry a six-month delay, I think this committee should be given a six-month delay.

If I could do it, I would ask the chair if we could introduce a motion for the committee to vote on, asking the staff to explore giving us a six-month delay in the report.

DR. SAMET: I will say, I won't classify that as a clarifying question. I think that the issue of the report and the schedule is something that we can come back to. I certainly agree with the herculean. Even with a six-month delay, it still sits at that level. I think the question though -- obviously, the report that is submitted on that time frame is a report that can be developed, and there might be recommendations for further study, for example, on particular issues.

Actually, just to follow up on one of the issues that Greg raised.

Is the fact that materials have not been received in response to a particular question at this point mean that they won't be received or that perhaps in the information that you're still sifting through, there may be relevant information? Because I think that for some of the questions for which apparently the slate is clean, we may well be -- it would be unfortunate if we did not have submissions.

DR. HUSTEN: As I mentioned, we've received submissions from all but one company that indicated that they would have a delay in submitting. So other than what we're getting from that one company, and we do not know what is yet to be submitted from that company, everybody else said that -- didn't provide any documents. And that one company has to date not provided any documents on these five questions.

DR. SAMET: So just to clarify, those companies that have submitted regard their submissions as complete at this point.

DR. HUSTEN: Yes, that's true.

DR. SAMET: Okay. Dan?

DR. HECK: I didn't note all of these questions you mentioned here, and I don't have those before me. But do you mean to imply here that no information has been received in response to these requests for information? Because it's my understanding that hundreds of pages of information directly responsive to these requests for information have indeed been submitted.

DR. HUSTEN: There were 16 questions, and we have received documents other than -- the documents that we received indicated that there were no documents for these questions. So there were responsive documents to the other 11 questions.

DR. HECK: Okay. So if the relevant information does not exist, then that answer is fully responsive. I kind of got the sense from the presentation that the companies had not been responsive, but there just --

DR. HUSTEN: They --

DR. HECK: -- in fact, is no information

on some of the questions, apparently.

DR. HUSTEN: Well, all I can say is no information was submitted on those five questions.

DR. SAMET: Patricia?

DR. NEZ HENDERSON: No.

DR. SAMET: Other clarifying questions for Corinne?

[No response.]

DR. SAMET: Okay. Thank you.

Next, we'll hear from Allison Hoffman.

FDA Presentation: Status of TPSAC Information Requests

DR. HOFFMAN: Good morning. What I'm going to be providing today is an update on the menthol white papers. If you recall from the March meeting, there were seven presentations that presented on initial findings of ongoing work. One was an original analysis, and there were six reviews of peer-reviewed literature. At the time, this was based on 343 articles in the NCI Bibliography of Literature on menthol in tobacco, which was done in 2009, plus 23 additional studies

found by CTP.

Presentations were on the use of menthol cigarettes by demographic groups. That was the original analysis; menthol sensory qualities and topography, consumer perceptions of menthol cigarettes, menthol cigarettes and smoking initiation, menthol cigarettes and nicotine dependence, menthol cigarettes and smoking cessation, and possible health effects of cigarette mentholation.

As known at the time, the March presentations were not comprehensive and the work was continuing on the seven topics. An invitation was issued to the public, research community, tobacco community and TPSAC members. So an invitation was issued for people to submit information regarding additional sources for possible use in the menthol cigarette white papers. This is actually an ongoing request, so if anything new comes out that you think TPSAC members should be appraised of, please submit them to the TPSAC e-mail address listed.

CTP received recommendations from several sources, including TPSAC members, the research community and the tobacco industry. Studies were evaluated for appropriateness to the topic. An exhaustive inclusion of research on the safety of menthol as a food ingredient additive was not cited. There were several studies that were included as examples to support the accepted supposition that menthol is generally regarded as safe in foods.

Review articles, most of them were not included in deference to original sources. However, a few were used to make general statements and/or provide background information. Studies that could not be adequately assessed were excluded. This included conference abstracts and plenary addresses.

Articles on menthol alone in humans were generally excluded since the focus was on menthol and tobacco. An exception was on the possible respiratory effects of menthol because menthol has been suggested to alter the respiratory effects of

tobacco smoke. Research that didn't examine menthol as an independent factor was generally not included except as examples of research deficiencies.

Research that was not specific to menthol, such as general tobacco use, was generally not included. They were included only in giving very general introductory statements, such as tobacco use produces a myriad of negative health effects and has caused more than 500 million premature deaths through disease such as cancer, cardiovascular disease and respiratory disease, with the MMWR citation.

Through the continued work of CTP staff and the information received, additional studies were included for all topics reviewed. This table presents a summary by topic, and the number of references that were used at the time of presentation versus what were used in the white papers that were submitted in your background material. For the use of cigarettes by demographic group, again, this was mostly CDC

analysis, and so this was considered a separate paper and not a review paper.

As you can see for the rest of the reviews, there were additions in references in all of the papers. You should note that there were significant increases in menthol sensory qualities and topography, as well as possible health effects of cigarette mentholation, but there were increases in all of the chapters,

Based on the information received, there was some modifications. For example, in the health effects white paper, for our first example in the presentation -- had one case control study. The author suggested that male menthol smokers have a modestly increased risk in pharyngeal cancer, odds ratio of 1.7 with a 95 percent confidence interval of .8 to 3.4, not statistically significant.

In the white paper, this was another case controlled study, suggested a small positive association with pharyngeal cancer in menthol smoking males but not females, again giving the

odds ratio statistics, but this difference was not statistically significant.

In our second example in the presentation, data regarding menthol and cancer suggests a possible menthol by gender by disease interaction. In the white paper, overall the data regarding menthol cigarette smoke and cancer do not support a link between menthol cigarette smoke and increased risk of cancer. However, there are some limited data that suggests possible menthol by gender by disease interactions.

Clarifying questions?

DR. SAMET: Allison, can you just say -- I think there are potential publication plans?

DR. HOFFMAN: We are looking into that.

DR. SAMET: You're looking into that. Okay.

Dan?

DR. HECK: Dr. Hoffman, I think you said on the exclusion criteria that research that didn't examine menthol as an independent factor was generally not included. Was that criterion

applied in the cessation studies and the addiction studies as well?

DR. HOFFMAN: Yes, because if, for example, someone was looking at a group of smokers and they did analyses based on racial and ethnic differences, and then made the supposition that perhaps menthol could play a role because menthol is more common in certain racial ethnic populations, that was not included, or it was given an example of something that we couldn't include because it did not examine menthol as an independent factor.

DR. HECK: But an example of, let's say, a cessation study for NRT or counseling or one of the traditional therapies, if menthol was not an independent variable in the experimental design, would those studies be excluded then by this criterion?

DR. HOFFMAN: Based on the example that you just gave --

DR. HECK: Yes.

DR. HOFFMAN: -- and the example I just

gave? Yes --

DR. HECK: So such as the study of --

DR. HOFFMAN: -- they would have to look at basically menthol use versus people who don't use menthol. Yes.

DR. SAMET: Greg?

DR. CONNOLLY: Allison, just trying to get a point of clarification. On your second slide, you list the presentations, what they were on. And there are specific consumer perceptions of menthol, which could mean perception of effects or perception of marketing, sensory qualities, which could mean topography but also could mean olfactory effects on the brain or on tactile receptors.

But when I come to -- and this is just a matter of clarification because I just think we've got to be disciplined in what we look at and have a common lexicon. And then on your slide, differences and references, the topics seem to change a bit, where we have menthol sensory qualities and topography. I would just limit

menthol sensory qualities to topography. And then consumer perceptions, it's really not marketing, but it would be perceptions of chemosensory effects and marketing.

So I think it's important we have a common lexicon as we walk down the road here. So what you're saying, we understand, and the groups in UCSF representing can understand.

DR. HOFFMAN: The reason why there's a disparity between the two is that this slide is based on the actual titles, whereas the others were based on the titles of the presentations in March.

DR. CONNOLLY: And these titles were chosen by the staff of the FDA for authorship?

DR. HOFFMAN: For the most part, yes.

DR. CONNOLLY: I think I would go back and --

DR. HOFFMAN: The CDC one is by CDC.

DR. CONNOLLY: If this is the committee's report, if the committee is going to write this report, then we go back and we look at those

questions that we spend a long time framing at the first meeting and that we published in the Federal Register, to see what match-ups we get. I don't think that's a difficult task. But just so that we have a common lexicon here and we have a common direction in terms of how we're going to synthesize this science.

DR. SAMET: Just to follow a point, maybe the menthol subcommittee could remember that these issues of terminology and perhaps, Greg, some sort of glossary would be valuable --

DR. CONNOLLY: Yes.

DR. SAMET: -- to include in the report. And, obviously, words have been used in different ways by different people and bring some clarification.

DR. CONNOLLY: Just a point. We have learned a lot over the past two meetings. There's no question. We have enhanced our knowledge greatly, and I think now we've got to take a few steps back. And what we thought we knew before those meetings now possibly has changed, and we

can reformulate around that.

I guess the second question, too, would the subcommittee be expected just to take what you have presented from NIDA or CDC's perspective or will the subcommittee look at those studies? Will we have an opportunity to talk to the authors of some of those studies like Eckels or Cabal (ph), even Leffingwell, who's an industry person? Will we have the opportunity to engage them beyond just --

DR. SAMET: Yes. I mean, I think the subcommittee will develop its own processes. The subcommittee can't I think probably have talked to people privately. I think any discussion of a subcommittee with anyone would have to be in public. But, certainly, we would not be constrained in our information gathering by these reviews. They're certainly a helpful starting point.

DR. CONNOLLY: Great.

DR. SAMET: Other questions for Allison?

[No response.]

DR. SAMET: Okay. Thank you.

DR. HOFFMAN: Thank you.

[Pause.]

Update on Menthol Report Subcommittee

Standards of Evidence

DR. SAMET: Okay. I'm going to do two things. First, I'm going to give a report of the menthol subcommittee meeting, which was largely by Web, held on September 27th. And in a way, this is a little bit redundant since I think almost all of the members of the full committee are members of the subcommittee for the menthol report.

So this is the outline for the menthol report that includes modifications based on our discussions, along with a listing of those who have agreed and are interested in being engaged in development of different aspects of the report.

So there'll be an introductory chapter, of course, and that will be combined with a description of the approach to writing the document. So not surprisingly, there will be an introduction that will provide the framing. I

think some of that relates back to the general charge that Corinne already mentioned, and there's a statute here to which we are responding.

This is material that we would hope to be able to develop relatively quickly. So this, of course, is something in the end that would be looked at by the full subcommittee and then this committee.

Going with that -- and this will be part of what I'll turn to in my second presentation this morning, will be our approach to gathering and reviewing evidence and how we're going to classify the evidence. And that's a topic that I'll talk about in general and then with some specificity in my subsequent presentation. And, again, I think you can look at who will be involved in writing these different components.

Third, physiological effects of menthol, some of the topics that will be covered within this chapter are listed below. And again, you can see those who will be involved. Neal Benowitz is not here with us today but will be joining us by

phone tomorrow.

A descriptive chapter on patterns of smoking of menthol cigarettes. And, again, the writing group is listed. Consequences of menthol smoking for initiation and cessation, there's a writing group. This chapter is where we intend for the moment to place marketing. And for this or for any other chapter where the subcommittee feels that additional expertise is needed, there's the opportunity to seek such individuals.

I guess let me get my terminology right, special government employees. Am I right on that?

[No response.]

DR. SAMET: I'm even learning -- the SGEs, that could be brought in to provide assistance.

Then the effects of menthol on risk for those diseases caused by smoking, toxicology, biomarkers, again, the writing group members. And public health impact, an important chapter bringing together and addressing that bottom line that Corinne reminded us about, including the need

here to address special populations, which might be covered in each chapter and, then as well, the information brought together here. Possibly to address contraband, and again, there might be a need for additional expertise related to that topic.

Then, of course, committee conclusions and recommendations, and again, remembering our charge to address special populations. And bringing this together would be a task for the whole subcommittee and, obviously, with TPSAC input.

So this is the outcome of our discussions on September 27th. I think a good reminder that Greg has now put this into the herculean category. And, obviously, there's a lot to pull off and develop. And I think, again, this will obviously be done within the real world constraints of how much can be done in the time available.

So that's a quick updating on the subcommittee's report. And let me ask then if there are questions or additional comments at this

point.

[No response.]

DR. SAMET: Okay. Then hearing none, we'll move on.

So here I'm going to turn to the issue of reviewing and classifying evidence. This is an important topic, and I think relates not only to the menthol report but the other reports that this committee will be developing. I think it's important with regard to sort of setting out our operating approaches to gathering and reviewing evidence. I think in Allison's presentation, we already heard about several systematic reviews.

So what I'm going to do is spend a little bit of time giving somewhat of a primer on systematic reviews and evidence classification, in part, so that we at least have a common grounding in these methods and a common vocabulary.

So just first to start, evidence, what is evidence? Well, here's one definition, and I'm just going to show you a couple. It's essentially what we know. Here, a definition from the

Dictionary of Epidemiology, “Results of research used to support decision-making.” I would actually argue that it’s the knowledge that we have gained through research. It might be used to support decision-making. Certainly, that’s true in epidemiology.

Turning to that great new source of information, here’s a definition from Wikipedia. “Evidence is information such as facts” -- here, notice I’m not sure I would have done this myself -- “coupled with principles of inference.” I’ll be talking about principles of inference. That’s how you decide from the evidence you’ve gathered what you’ve learned, that act or process of deriving a conclusion. Of course, scientifically, we are interested in developing evidence that might disprove a hypothesis.

But let’s take evidence in a working way as what we know, and then the flip side of that is what we don’t know, uncertainty. And this is a recent important report from the National Research Council, Science and Decisions, in a sense, an

updating of the famous Redbook report on risk assessment published in 1983. Uncertainty, what we don't know, lack of incompleteness of information. Uncertainty depends on the quality, quantity and relevance of data and on the reliability and relevance of models and assumptions.

So when we look at evidence and uncertainty, our task in developing evidence for decision-making is to try and say what it is we do know and what it is we don't know, and to describe what we know in some uniform and useful way, and also describe what we don't know in some uniform and useful way. And, again, for example, the surgeon general's reports and some of the other models for decision-making I'm going to take you through provide evidence classifications that describe the strength of evidence. And in various settings, there are various descriptors of uncertainty. There are mathematical ways to try and describe the degree of uncertainty, and some of these tools are useful.

As a committee, I think we need to think about both evidence and uncertainty and how we will approach describing both. And I think it's important for us to do so in a uniform way so that when we say that uncertainty is moderate or there's little uncertainty, there's some basis for using those terms.

Now, historically, one of the early evidence-based reviews was the surgeon general's report of 1964. This is, of course, the presentation of the report by then Surgeon General Luther Terry, and there is the report.

For those of you who haven't read it, I think it's quite a remarkable document. It was a systematic review. The committee was a broad group of scientists and people trained in health who were asked to review all the relevant evidence, evaluate it and reach conclusions. And they set out a framework and system for doing so. And, in fact, the so-called guidelines for causal inference, or criteria for causal inference, that came from the surgeon general's report are still

in wide use, not only in relationship to risks of tobacco but widely used, for example, by the Environmental Protection Agency and their weight of evidence guidelines for various adverse health effects and incorporated by others.

So just as a reminder, the consistency of the association; that is, as studies were done in different places, different populations, by different investigators, were the findings the same? The strength of association. How large was the association, the effect; the idea there being that stronger associations were less likely to have extraneous non-causal explanations.

The specificity of the association; that is was there a unique one-to-one relationship between the cause, say, smoking and the outcome. This one proved to be not particularly useful. We know, for example, that smoking causes many diseases and many of our chronic diseases have many causes. So, in practice, this one does not turn out to be very important. To give you an idea of a very specific association, asbestos and

mesothelioma, most cases caused by a single exposure.

The temporal relationship, easy, cause needs to come before effect. And then coherence, does the whole story fit together? Does the epidemiological and biological information stand together? Do external facts fit with the hypothesis? Lung cancer rates are rising. Did smoking rates rise before or after that rise in lung cancer, for example. So these guidelines are still in use.

In 2004, the 40th anniversary report returned to this topic. We've distributed chapter 1 from that report, which has a relatively extensive discussion of causation and guidelines for causal inference, so I think useful as an update. And, in fact, in that report, there was an attempt to set out a uniform classification of strength of evidence. And I want you to look at it not as a model for this committee only in that it gives a hierarchy of certainty of strength of evidence, so Level 1, sufficient; 2, suggestive;

3, inadequate and 4, suggestive of no causal relationship. The main point being that here's a standard approach that is being proposed.

So if we look at public health -- and, again, that's our sort of bottom line here, this is something that I show to the medical students when I talk about how we proceed. We search for problems; that's where we do public health surveillance. We identify the causes of those problems. We understand how big the problems are and who they affect. We develop policies and interventions. And then we try and understand through reassessment if we've made a difference. And then the tools coming down here are surveillance, looking at mortality data, for example, or tracking prevalence of smoking. We do research. We identify causes by doing research and bringing evidence together in these systematic reviews and applying guidelines. We do risk assessment and then go on to policy tools, and continuous surveillance to see what has happened through our interventions.

Now, just to show you an example of such a process, this slide outlines the way that the Environmental Protection Agency is evaluating evidence at this point for the major air pollutants, the so-called criteria pollutants. This is Sections 108 and 109 of the Clean Air Act. And I show you this only as an example of a description of an algorithm for looking at evidence, reviewing it and making decisions. And, again, I think as we move forward as a committee, I think we want to make certain that our underlying approaches are always clear and laid out.

If you look over here -- this side is where the scientific evidence starts to be developed through workshops and other processes. It's assembled in a integrated review process, evaluated, and moves on through various sort of policy relevant steps until in the end an air quality standard is developed.

Now, again, the Environmental Protection Agency has in this instance moved to a uniform

classification of strength of evidence. This is, again, around causation as the target, related to the various pollutants, whether it's ozone or particulate matter. And, again, you can see a hierarchy going from a causal relationship through, again, parallel to what I showed you of the surgeon general's report but now with several categories describing the strength of evidence.

Again, this next slide describes sort of the paradigm of evidence-based medicine. Now, there's a lot of discussion about using so-called evidence based medicine approaches to guide clinical care, and, again, another evidence-driven process. So I'm just trying to show you some examples that will help us as we think about what we're going to do.

So what is evidence-based medicine? Well, we do research, lots of it. And we assemble that research finding to look at what we know. We do our evidence-based reviews. We put the evidence together, do systematic reviews. These typically are looked at by expert panels leading

to guidelines, and then we have to learn about how well those guidelines work, doing so-called effectiveness evaluation. And, again, these days, of course, we hear a lot about comparative effectiveness, meaning in relationship to each other, how well the different approaches to therapy or diagnosis work. So another example of an evidence-driven process.

There will be a test at the end of this, by the way.

Then, again, this looping to always continually evaluate what has been happening. So, again, the analogy in public health would be the surveillance that we carry out.

So, again, what's a systematic review? Well, I think already you heard from Allison about the approach that FDA has taken in putting together these white papers, identifying all the relevant evidence, using a transparent strategy. So whatever is done to gather the evidence needs to be clearly described in a way that if somebody else wanted to redo the review and evidence

gathering, they would end up hopefully with the same pile of evidence. That doesn't always happen in practice and there's some interesting empirical work here, but that is the goal.

The evidence is put together in so-called evidence tables so you can look at it, and then the evidence is evaluated in some uniform way with a protocol, looking, for example, systemically at the strengths and weaknesses of different studies and deciding how to pool the evidence, how to put it together. And that's often a place where expert judgment holds sway. It's also one where quantitative synthesis might be used, so-called quantitative meta analysis or meta analyses.

Now, I'm going to give you one more example that I think holds perhaps a more specifically useful analogy for us. I will say that this is where Dr. Deyton and I first crossed paths when he was at the VA, and I chaired an Institute of Medicine committee that was charged with addressing this task, presumptive disability decision-making for veterans. Now, what that

actually means in terms of the framework I've discussed was how should VA make decisions about compensation in the face of gaps in the evidence. And VA or the Congress makes so-called presumptions to bridge gaps in the evidence. An easy example with Agent Orange is that it is very difficult for an individual veteran who served in Vietnam to prove that he or she was exposed to Agent Orange. The VA made a presumption that everyone who was on the ground between '67 and '71 was exposed to Agent Orange so that everyone who fits those criteria, feet on the ground '67 to '71, is presumed to have been exposed to Agent Orange. That's a presumption. So we were charged with how to think about improving this process, which led us into looking at sort of the underpinnings of systematic reviews and classification of evidence.

So this is just a statement of the problem. I told you that veterans, of course, have multiple exposures that might lead to disease risk, and the question was how to compensate and

develop an evidence-based approach for compensating veterans in the face of uncertainty.

So this is what we recommended. So, first, again, at the framework, the key parts were making sure that --

[Pause for slides.]

DR. SAMET: I'll keep talking. So what I was going to show you there was sort of the information and evidence flows to provide a basis for decision-making. In the case of veterans, that really involved two streams of evidence. One was understanding and knowing what they were exposed to, and the second was trying to understand the risks of what they were exposed.

The next slide, if you could see it, would show you, in fact, the kind of process that we proposed for decision-making by the VA, which really had more to do with the kinds of committees and evidence flows that the VA would logically set up.

The next slides, which are the best ones --

[Laughter.]

DR. SAMET: So this is the one I was talking about. We were just talking about the information flows. And then the next one is sort of the process we proposed.

Now, let me go to what's more relevant to us. So we proposed a decision-making process that would be evidence-driven, and we proposed a four-level evidence classification and then some structure to use it. But important to our construct was the idea of equipoise, and this is a word that's been used variably across the biomedical literature and elsewhere. But in describing evidence, we might say, gee -- you might hear things like we're moderately certain, we're quite certain. With the word "equipoise," we're trying to at least define one clear point. That is the point where the evidence hangs in the balance; that as evidence is reviewed -- let's say it could be on causation, it could be on something else, a relationship, the evidence that hangs in the balance, that it's equal for or against.

If we go back to look at the classification scheme that was proposed by our committee, we said that the evidence could be sufficient. Sufficient includes that a causal relationship exists. We said the evidence could be at the balancing point or above, but not reaching the point of sufficiency.

Now, what we were trying to do here was to provide a classification scheme that we thought would be useful to VA in making a decision, that evidence very often does not reach the level of sufficiency. And, in fact, if one were watching a group of veterans to understand their disease risk, you might now know enough, in fact, until quite a large amount of time had passed. Perhaps disease risk only manifest late or the evidence is accumulating and hasn’t reached certainty. So we thought that by saying that the evidence was at the balance point or above, that that might be a point at which VA would consider compensation to be appropriate; that is, sort of from the point of a tie, the evidence is equally for or against an

association, or above, compensation would be appropriate. So we were trying to set out a scheme that was useful to the decision that needed to be made.

So equipoise, this idea of balancing the evidence -- and it's sort of -- we're often confronted by trying to evaluate evidence where the answer is not completely in. And I think you can all see, well, we sort of go -- this is sort of the two-handed scientist story, on the one hand/on the other hand kind of story. And I think as we described evidence, we often know sometimes we're sort of at this balance point, and that's at least a useful point to be able to describe. And then as evidence accumulates, it might tip that balance one way or the other.

Now, I'm going to show you some pictures, and the committee's report included pictures as a way of describing how much we know and sort of where our belief about where the answer lies. So this slide shows the idea of the strength of a cause -- so in this case I'm dealing with cause,

but this could be something else -- and if there is no effect, our estimate of the causal effect, our coefficient beta from, let's say, some regression model would be zero. An increase in exposure to air pollution does not increase risk for lung cancer, let's say. If there's no increase, the estimate of the causal effect is zero. As the effect becomes stronger, our beta, our estimate of how much the increase is, gets bigger.

Here in this graph is a plot, an expression of where -- in this case, let's say an expert or a mathematical model or a group of experts think the answer lies as to how much of an effect there is. So this is the probability distribution of where the true effect of beta might be. So if you summed up all this stuff under the line, it would be one by definition.

So if you look at it, in this case, there's a little bit of possibility that there might be no effect. So there's a little bit of our probability mass put on zero. But most of it

is out here stretching well above zero and centered out here at some effect that's quite non-zero. So keep that one in mind.

Then here is a different shape. So in this one, there's a little bit more belief, as you can see, more probability piled up that there could be no effect and still substantial credibility given to the idea that there is an effect and one that might be, in fact, relatively strong. And it's strong as in the prior distribution.

Then one more. And here now, there's a lot more belief or credibility given to the possibility that there's no effect but still some to the possibility that there is an effect. And this might be sort of something that looks like our equipoise idea.

Then here's another one where most of the probability is put around the possibility that there's no effect with some idea that there could be a small effect.

So again, just to go back, talked about

the idea that as we look at evidence, we may have, as a group or as individuals, a view about where the balance of the evidence, the strength of the evidence lies for a relationship between one factor and some outcome. There's a point of balance, this equipoise point where the evidence for equals the evidence against. And that as we look at evidence -- and I think this will come up with any group as we look at it. Some of us will say, gee, the evidence looks pretty strong; some might say, well, but I'm worried about this, I don't think it's as strong as you do, and so on.

So there will be a distribution within a group of experts and this kind of thing has been studied, putting evidence in front of experts. Of course, you get a distribution of beliefs about the strength of evidence. But here's an example where most of the evidence -- most of the credibility is given towards having some effect with a small possibility that there is no effect, and then one where there is less certainty about there being no effect but still relatively strong

credibility for an effect. Here's sort of a 50/50 kind of distribution, and then here's evidence showing no -- one showing little credibility for an effect.

So I put together three slides for discussion. And what I'm going to do, I'm going to show you these, and then I'm going to sit down and we will talk about these.

So, first, evidence reviews. So we have four sources of evidence. We have the peer-reviewed literature; we have the industry documents that we'll hear about today; we have what we received from the request industry; and then, of course, public input.

So for the peer-reviewed literature, I think our approach should be a systematic review process. And if we deviate from a systematic review process, we need to spell out I think very carefully how we are going to bound the evidence that we're going to review and not review.

For the industry documents -- and again, as we'll hear today and I think you probably

should have read in the UCSF white papers -- there are approaches for reviewing the industry documents, search approaches, the snowball approaches that are used. The request to industry, the review there is in progress by the FDA staff. I understand there's a lot to look through. And then, of course, the public input as a source of further, specific evidence.

Now, how do we classify the evidence? So first, what is our target? Well, as a first point, our target is really whether there is a relationship and not necessarily causation. We're going to be looking at a wide variety of types of outcomes, a wide variety of questions. Public health impact, for example, as an outcome is one that is very broad, so the word "relationship" or "association" may be more appropriate. We may want to define our target as we move through, but it's not necessarily causation as has been, let's say, the topic of the surgeon general's reports where there are often very specific questions about does smoking cause this or that disease.

The criteria for evaluation should at least remain with some of the well-used criteria for looking at strength of evidence. Of course, temporal relationships should be appropriate, consistence of the evidence, the coherence of the evidence and its strength. And then the classification scheme that I would suggest is one that is based around this principle of equipoise, which at least gives us a way to center our evaluations of strength of evidence.

So here is some potential wording for a classification scheme, again, based around strength of evidence and this concept of equipoise. So, again, what we would like to do is classify strength of evidence in a way that will be useful for FDA as it does its job. So I'm suggesting here for discussion at least four levels sufficient to conclude that a relationship is more likely than not, so that's evidence sufficient to put the belief above the equipoise point, the 50/50 point; the 50/50 point itself, sufficient to include the relationship is at least

as likely as not; insufficient to conclude that a relationship is more likely than not -- I guess actually that includes the equipoise point, but we may have to reword this -- and then insufficient evidence. I mean, it could be that we look at something and we just don't find much evidence there.

So just to recap a little bit and maybe to take us back to here for discussion, I've taken you through some historical examples. We've talked about what is evidence and uncertainty, and I think expressed my view at least that we need to be quite uniform in approaching our job as we describe what we know, i.e., evidence, and what we don't know, i.e., uncertainty, that there are processes, examples, that can serve as useful models for us. There are multiple different kinds of sort of hierarchical classifications of strength of evidence that are out there.

I think that the Institute of Medicine's report, the concept of equipoise is a useful one for trying to center our classification in showing

what we mean in some useful way as we use words like “sufficient” or “not sufficient,” that it’s based around this more likely, or at least as likely as not, point.

So let me stop. I think we should have discussion of this. I think this is a very important aspect of our work as a committee. So what we might do, I’m going to suggest we turn to this first since it’s been -- I’ve just covered. I think it’s important. I think we’ll probably need to spend a fair amount of time having this discussion. We can come to the menthol subcommittee report and see if there are additional thoughts about that.

So let me open up for discussion.

Dorothy?

DR. HATSUKAMI: Jon, in terms of some of the committees that you have been involved with, did they discuss the quantity of evidence? I would imagine that the amount of evidence that you need would be dependent upon the nature of evidence, because in some of the topics that we’re

going to be covering, there isn't sometimes a lot of evidence.

DR. SAMET: I think what you're suggesting, in a sense, the answer is yes and no. So to rephrase your question in a way is, is there sort of standards and guidance for how much evidence you needed in saying how many studies that there are or how much is there. And I think the answer is no. I mean, so much of this is done in sort of a contextual way because I think the answer is you might have sort of a homerun study or finding, and it perhaps takes very little to reach a conclusion. I mean, how would you not act, let's say, with the early findings on diethylstilbestrol and the adenocarcinoma of the vagina in young women. I mean, there are examples like that. So I think my comment would be that's sort of a universal answer, it depends.

Jack?

DR. HENNINGFIELD: Where we don't have evidence, where we've made requests to the industry and have not received evidence, I'm

trying to figure out how we handle that in the decision-making process. And in some cases, for example, if a question is does menthol contribute to dependence, some of these categories of information that we've asked for, how much is there, why did you put it in, what was the basis, it would be helpful, but it's not critical to answer that question.

So if we do not get the evidence from -- if we don't get the information from the industry, we just go forward without it or what's -- I guess I'm trying to understand the process. Are we hostage to the industry not giving us information to make decisions or do we just make decisions on the basis of the evidence that we have on the timeline that we have?

DR. SAMET: So let me reframe your question because I think the more generic issue is, if evidence is not available, what can we say or we can do? And I think if you sort of move down to that fourth category of evidence that says it's inadequate -- and it might be inadequate

because it's not been provided. It might be inadequate because it does not exist, and then I think we're pointing to a gap that needs to be filled with research.

I think if we reach a point where we're at that insufficient evidence, that bottom line, it could be that that means that more information should be sought from industry. It could also mean that there's perhaps a research agenda that needs to be addressed or that there are data sets that need to be explored.

So to me, if there's an important question where we get to that point, then what we as TPSAC can do is say this gap ought to be covered and here's some ways to cover it.

We can only respond to the evidence that we have in hand. On the other hand, I would see it incumbent on us for important evidence gaps that we suggest how they could be filled.

Cathy?

DR. BACKINGER: I guess to follow up on Dorothy's question, which was about quantity, mine

is about quality. So have you considered how you're going to review the quality of the -- whether it's peer-reviewed or not, because of pilot studies, for example, but also input from the public and from the tobacco industry as far as methods and coming up with what to include in the review and what gets kicked out.

DR. SAMET: So I will comment. I think others may want to comment. I think clearly since we're just getting started, I don't think there's a strong answer to that yet. In general, for epidemiology approaches for quality scoring of observational studies, for example, are not particularly successful. There have been attempts to try and do this. I think if you move in the clinical trials realm, it's perhaps a little bit easier.

I think when we move on to the writing committee phase, I think each group will need to evaluate the most important articles for strengths and weaknesses. And I think within the categories of the kinds of articles, I think each group can

say how they're going to evaluate them.

I think in the time available for this report, the herculean report, the possibility of taking what might be hundreds of studies and evaluating each one in a uniform framework is probably off the table. I think that's probably not realistic in the time frame available, and I think there we'll have to rely on our readings by the subcommittees, the judgments that have been made by others to select and choose the most important articles based on the subcommittees' evaluations.

DR. BACKINGER: And I would assume then that that would be a transparent process as well, that you would clearly delineate kind of the exclusion/inclusion criteria and what was considered.

DR. SAMET: Yes, I think transparency has to be sort of a watchword here.

Tim?

DR. MCAFEE: Thanks. I thought I would just try to complicate things a little bit more in

terms of adding to your model really around the issue of how we delineate the “it depends” question. How do we decide, once we’ve arrayed and analyzed the strength of the evidence, whether it’s sufficient or insufficient?

I think the analogy that I’m struggling with around this is sort of like, well, what universe are we living in? For instance, if we were to go on with your medical one, are we living in -- is the question that we’re asking more like do we institute an asymptomatic screening test and aggressively implement it for the entire population, or is this question more like a tertiary treatment issue in oncology? And in the former, you’re going to want very, very, very, very strong evidence for no harm and benefit. And in the latter, you’re going to want good evidence for benefit, but you’re going to accept a lot more possibility for harm than you would in the former.

So I think we need to think through, and I don’t think it’s going to be the same for every question that we answer around this. But there

may be some for instance where it's going to be more like oncology because we've got a situation where a half a million people a year are dying from something that's already happening. So this isn't like instituting a new drug. This is something that the consequences of doing nothing will be that things will continue in the status quo. But there may be other situations where we're introducing something new to the equation where we really have to be quite meticulous about understanding harm and benefit.

So I don't know what the answer is, but I think we should think about that consciously when we're tackling these questions and not just think about evidence like we would around a medical --

DR. SAMET: Yes. I think your question is a useful one, but in part relates to what FDA will do with the outcomes of the evaluations of the evidence. So what I think we want to have -- and I think we'll want to hear from FDA about these slides, this presentation, this morning -- is provide an evaluation in a useful way for

decision-making regardless of whether that is the need for particular regulation or the need for more research or public education or whatever the matter may be.

So we want to provide something that will be in a format that is useful. Some of the matters that you describe might go beyond in terms of other decision-making tools, perhaps, doing public health impact modeling or something else that would guide selection of approaches, weigh benefits against risks, harms and so on.

I think at this point in terms of sort of the specific charges for our reports and the menthol report in particular, what we need to do is evaluate the evidence, say what it is we know and we don't know around these questions and coming back to the overall public health impact charge, and then, in a sense, try and provide something that is useful. And I think we do need to engage the FDA in our discussion this morning.

Let's see. I've got Mark.

DR. CLANTON: Dr. McAfee actually

anticipated an issue I was going to bring up, but I'm going to further simplify it. When it comes to making policy or decision-making in health care, there are really statistical lives and there are actual lives. So statistical lives are the people who might get a disease because they're exposed to a certain set of risk factors, and actual lives are the people who ultimately end up with a particular condition because they were exposed.

In terms of the evidence, though, this is relevant actually even the pre-FDA phase because association, which has more to do with statistical lives and making policies, or at the statistical public health level, we might want to say do we want to look at associations maybe more strongly than we would normally do because maybe there's better evidence along the association line versus the actual lives, which is a person who has these three conditions will absolutely get the following disease, and you need that kind of evidence at the clinical level.

I don’t know that we’re going to find that causal kind of data yet, given what we’ve seen thus far. So it is relevant to understand whether we’re looking at statistical lives and policy or whether we’re trying to give advice to an individual who has a certain set of conditions. Again, I don’t know how to process that yet, but I think Dr. McAfee’s point is we probably need to understand exactly how public health versus the medical level of decision-making happens.

So my second point has to do the report itself, and it turns out language is pretty important here. So on the issue of the evidence, where we don’t have enough, whether there isn’t causal enough evidence, whether associations are equipoise in the balance, it’s relevant to understand whether we’re producing the report on menthol, which is meant to be comprehensive and end-all/be-all, or whether we’re producing a report on menthol. And that implies some sort of interim; here’s where we are with the evidence, and here’s what we can say today about the

evidence. And, of course, your point about here's where science needs to go in order to understand more causal type of connections.

I think we need to understand that because we've already had good arguments as to why this might be postponed or extended. You made the point that, in fact, we can't possibly look through every single piece of evidence and even grade it. So the question is, is this the report on menthol, is this a report on menthol? And quite honestly, if it were the latter, it gives us more flexibility in terms of just saying here's what we know and here's what we think versus this is the end-all and be-all on menthol.

DR. SAMET: So I think it's a useful way of framing it, and I was waiting for you to say after you said "the" report to say "a" report because I was going to say yes. And I think that, clearly, this will likely not necessarily be the last report done on menthol. I mean, we don't know where we're going to end up, so I think I have to be cautious about saying there's going to

be more reports or further evaluation, but I don't know why this would necessarily have to be cast as the report.

We know that there's a limited time frame and that evidence will continue to be forthcoming. Perhaps there will be recommendations for research, because, in part, this is not as highly studied a topic as one might have expected, considering how widespread these products are. And we heard from Allison about the reviews. Well, they're certainly relatively small numbers of studies compared to tobacco and cigarettes in general. So I think your point's a good one.

DR. CLANTON: I think that's helpful because it actually gives us a little bit freedom and flexibility in terms of doing the work which is required for March 23rd, 2011.

DR. SAMET: Right.

Dan?

DR. HECK: I guess scrolling back a few questions to Jack's follow-up on the FDA presentation on the questions, this is the first

I've heard from FDA on a response or a representation of the quality and quantity of the information that has been disclosed so far. And, again, my understanding of that information is that it was quite voluminous.

Certainly, if there is a sense -- and I think all the major companies, certainly the ones that hold the majority of scientific and other data of the sort that's been requested -- my sense is, which I think is accurate, is that all those companies have expressed a willingness to cooperate, to provide additional information, clarification or anything else the FDA may require.

I do sense that there are some of these questions, there really isn't responsive information. In other cases, certainly, if FDA requires additional clarification or information, I think the companies have expressed a willingness to provide that; just we'd be glad to have a dialogue on that.

DR. SAMET: Thank you.

Let’s see. Jack?

DR. CONNOLLY: I think I was before Jack. He already asked a question.

DR. SAMET: Oh, he did. You’re fighting over --

DR. CONNOLLY: No, I’m sorry.

DR. SAMET: That’s all right. Go ahead.

DR. HENNINGFIELD: I want to go back to Dr. McAfee’s point about benefit because I don’t know how we can make recommendations without factoring in benefit. And this is also related to the absence of information that industry has provided. And my question is part of the process, and what we have is a concern about menthol or the committee wouldn’t be charged, wouldn’t be here. We have a sponsor, an industry, that desires to keep menthol on the market.

Now, a number of us have served on advisory committees for drugs. If it was a new drug application, the industry has to justify the benefit and it has to address the concerns. And if it says we don’t have information that has been

asked for, then the industry doesn't get the application approved.

The same works if it's with respect to a product that is already on the product. Think of Vioxx, where the FDA had to consider is there a concern that's sufficient to take it off and/or is there a benefit that should be considered. This happens all the time. It happened with OxyContin. There were serious concerns. In that case, a path was found to keep it on because of benefits.

But you can't make decisions about whether or not something should be there without factoring benefits in. And so I'm wondering how we do that. And in the case of information that isn't provided when it's asked for, I don't think we should be hostage to that. Then the concern should predominate or should prevail. That's what would happen if it was an application for a new drug or to keep a drug on the market. And if this process is radically different, then I'd like to understand how it's working.

DR. SAMET: Well, Jack, I think your

point is a useful one. And as I've sort of developed similar materials that I've sent to the committee, I've asked FDA if there were models or precedents that we could draw from because, as you point out, if you bring something, a new drug on the market, you look for a pivotal clinical trial showing that, in fact, there is the anticipated clinical benefit. And let's say in the case of Vioxx or whatever, some other drug where adverse effects become evident after marketing, there may be then evidence of harm found through culling over an assembly of clinical trials or other sort of post-marketing surveillance data.

This does not seem -- these situations are not analogous, which I think is your main point, to our task. And I think that's why we are sitting here, in a sense, talking about very new things and setting what will be the precedents that will be used by the center as they meet the charge of the law. So I think we are on new grounds with a need to look at things like how are we going to evaluate evidence and put it together.

When you talk about benefits, in a way, our evaluations of the evidence and conclusions with regard to strength of the evidence are part of the building blocks towards deciding what are benefits, what are risks, how does this story come together. And perhaps some of what we're doing is as we look at finding the answers to the questions we have to address, those become pieces of broader decision-making. They might become pieces of models of public health impact that are used to guide the agency, models that are based on the evidence that we have in hand.

So I think our role, we are the scientific advisory committee, is to provide guidance on the science. And then I see in part that it's going to be FDA's job to take that science and reach the conclusions. I think where this discussion has gone that's useful is for us to try and bound what we can do in our reports versus what FDA might do; particularly as, let's say, they develop more capability and capacity in public health impact modeling and elsewhere.

These are decision support tools, and we're providing guidance on the science that will support that.

So that's how I would sort our role out versus what FDA itself will do. So as a committee, we're not going to be building models of population impact. On the other hand, we might well be providing peer review and guidance on the construction of such models. So that's how I would sort out our roles.

I don't know. Corinne, do you want to comment here on my trying to bound our tasks?

DR. HUSTEN: No, you're absolutely right. It's the committee's job to describe the scientific evidence and the strength of it to us so we can take that into account.

DR. SAMET: Greg?

DR. CONNOLLY: I'm a frustrated attorney. I think we've been given specific instructions by the Congress, both the staff of the FDA and this committee, to act. And it's not in our latitude to go beyond what Congress told us what to do.

Congress told us, immediately upon establishment of the TPSAC under Section 1917(a), "The secretary shall refer to the committee a report," which would include the science assessment, which we just described which could conclude that there's insufficient science, that the industry was not forthcoming, that more research is needed. And more importantly, which wasn't referenced, is recommendation.

Now, the committee is then going to synthesize knowledge, but in recommendation make translation of the knowledge into public policy, particularly as it affects high-risk groups in America who are suffering from high levels of morbidity and mortality. Within recommendation, it is both a science translation function but it's also a policy statement that can address issues while there's insufficient science. And maybe the precautionary rule should play here, until the science becomes sufficient. But it may not be just one recommendation. I could see the committee posing a series of recommendations. But

that in a sense is why we were formed by Congress. And for us to ignore that recommendation phase, I think is in violation of congressional intent.

The second point I would make is David Kessler when he was commissioner spent an enormous amount of time and staff on the 1988 rule. I think it's worth going back and looking at that rule to see how it was constructed, to see what the science base for those inclusions.

The court ruled that the agency lacked authority but did not address the content of the report, so we can still look at that report and see what direction that gives as well as the surgeon general's report.

FDA is unique from EPA. It's unique from the VA. It's unique from any other federal agency in that it can control any product from coming into marketplace. That's not true of any other agency in this nation, and it's there for reasons.

The 1938 law looked specifically at a response to poisoning of 88 children. And so authority is strong within this agency, and we

have to understand that and have the courage, in the sense, to exercise that authority.

The second point I would make is that -- and, Jon, I think your presentation was excellent. I might want to borrow your slides to teach people with that knowledge. The term that we are looking at is “likelihood.” That is the essential term in our decision-making. And you used that in the second-to-last set of slides. You put in likelihood. That’s what the law says, the increased or decreased likelihood. So case law on likelihood or what is stated in FDAAA Act on likelihood is essential to translation of that science into recommendations or to assessing that science. We have to understand that.

Unfortunately, many terms in the statute are more legalistic than they are scientific. Characteristic, and the only thing I could find on characteristic was if in their label they put vanilla as an additive, then all of a sudden that portion of the statute is nullified if the regulation predominates over it. Substantially

equivalent, that is not a scientific term; that is a legal term decided by the courts; likelihood.

So we have to start thinking of merging what our science is with the legal terms that are being referenced here. I think we should be as comprehensive as we can but be very careful of walking down a black hole around selective issues where we don't get a report out by March 3rd. I don't think this is the final report. I think this is going to be what do we have today, but the recommendations will drive what the agency should be looking at in the future, how precautionary we should be about menthol.

I apologize for taking so much time, but I think we have been told by Congress to carry out our job and our function, and we have to go back to this law and stay with what this law says.

One final point I would make. In 1988, David Kessler invoked the 1938 statute. And what he looked at was intent to affect the structure and function of the body. It directly related to nicotine. And to the extent that menthol and

nicotine are working somehow synergistically to affect likelihood, intent then comes in to play, in my belief -- and we should discuss this -- in this discussion, in this report; what was the intent?

If we go back to the 1938 statute, which enabled FDA in the first place -- and then we get back to Jack's point that even if we are weak in abuse liability, that is probably going to be the central question. The question of intent is going to come into abuse liability, and then our recommendations are going to have to deal with the ambivalence and the lack of evidence.

I apologize for taking so much time, but thank you.

DR. SAMET: Okay. Just maybe to cover a couple of the issues -- and again, I think we should continue some of the discussion, and I think you raised a number of issues that the FDA will have to weigh in on.

I think in our reviews, we have to rely on sort of the established processes for reviewing

evidence and classifying it as researchers and the scientific community and others do. I recognize that sometimes there may be apparent mismatches between what might be written in the law and what scientists do. And I think, actually, if you go back to the VA case, that was in the part the reason that the committee I chaired existed. It seems that the Congress may not have had the benefit of this lecture.

So I think that's the point. I think we have to be grounded in what we're told to do in the law, and I think we have to make certain that we explain our connections to it. So just to make that point, but I think the approaches that we apply have to be those that are used by our community in general.

Let's see. Who else? Yes, John?.

DR. LAUTERBACH: Dr. Samet, you mentioned peer-reviewed literature, and I'm very concerned that the search criteria that we see or literature criteria we see in the documents, that are in the briefing materials, the peer-reviewed literature

was not properly assessed. I keep coming across documents -- and I'll mention some of these later -- where, because of the limitations in the search criteria, the limitations of the database that's searched, that significant peer-reviewed literature was not included.

DR. SAMET: I don't know whether Allison or anyone wants to respond to that. I will say that the hallmark of what I think we should be doing is having as comprehensive search strategies as possible and stating what they are. Remember, my fourth stream of input to our information gathering is public input, and I think to the extent that as we report what we have found and what we're evaluating, committee members -- the public, defined largely, can provide us additional peer-reviewed information. I think that should certainly be forthcoming.

It is remarkable that in spite of our sophistication in information management, I think we all know from experience that you search for things in the literature, and you expect one or

another article to come up, and you do your search and it's not there. So these tools still have imperfections. And I think to the extent that we have other routes to bring evidence in, including public input, I think that would be important and something we will use.

Jack.

DR. HENNINGFIELD: In some areas, for example, intent, the intent of the industry, there you're relying on documents, so the concept of peer review probably isn't necessary to address that. The same thing possibly with respect to benefits, if there isn't peer review demonstrating benefits, then I don't think we're in a position to say that there is -- then I think we're in a position to say there is no demonstrated benefit. You can come to a firm conclusion. So I think that we have to look at the questions that we're asking to determine if peer review is a necessary standard, and I think in some cases it's not.

DR. SAMET: And I return to these four sources of information, which I think are general

categories, recognizing that some of this will not be peer reviewed. Perhaps there are other kinds of unpeer-reviewed reports outside the industry that may be relevant, and if they're brought in, we should be looking at them.

Maybe, Corinne, I wonder if you want to make any other comments or others with the FDA, David, Bop, will want to make any additional comments. What I'm trying to propose is something that hopefully will be useful as we look at sort of this science and beyond interface.

DR. HUSTEN: Sure, and let me just address the one issue that was brought up. We did ask for input about articles, and if folks know of other articles, continue to send them. We looked at everything we received. Some were not included in the white papers because, as Allison mentioned, they might have been studies that looked at African-Americans versus whites and a certain outcome without looking at the menthol cigarette use, or they might have been studies that looked at menthol in food in a way that didn't seem to be

relevant to this topic. But we encourage everybody to continue to send us articles. We're continuing to try to update as well, but we have looked at everything we've received.

Just as far as the framework, I just want to say that it will be very helpful to FDA to have some sort of framework on how you're assessing the evidence so we can clearly understand what you're trying to tell us about the strength of the evidence and that there's consistency across the chapter. So if you say something in one chapter, we understand it in the next chapter.

But I think what's really important is to provide the explanation and the rationale for why you think a certain way about one of the outcomes. It's at least if not more important than a specific categorization. I think the categorization helps because it helps us understand again what you're talking about, especially if you clearly define it. But the description of why you think it's above equipoise or whatever criteria you use is incredibly helpful

to us. So I encourage you to in your report flesh out why you think the evidence is sufficient or insufficient so we can understand it.

DR. SAMET: Certainly, I completely agree with that, and we might have naked statements and I think we'll make clear they were.

Greg?

DR. CONNOLLY: At the same time, Corinne, this is a communal process. But I would be very interested in criteria used by CDER, by Biologics, by other FDA agencies in addressing similar questions so that we can learn from the agency on how the agency constructs science. So if you can return to us with what the criteria used by other FDA agencies, I think that would be helpful. I do not think we are starting from scratch here.

The second thing is we can send articles, and if this is our report and we send articles, and the FDA says, well, we think this is okay and this is not okay, and we're going to make a decision staff-wise, and those don't get to other committee members, are we hampering the

function of the committee report? If we send you articles, can we send that to the entire committee and maybe even have it posted on the public record so that there's transparency, so we don't feel there's a filtering going on -- and I'm not accusing anyone of anything -- so we have transparency and we have dialogue among a group of people that form a committee.

DR. HUSTEN: If a workgroup has articles that they think they want to rely on in the report, send them in and we're not going to suppress them.

DR. CONNOLLY: If we send those to members of the committee and put them on the public record, is that the best way to assure transparency?

DR. HUSTEN: We've asked you to send them to us so we have a single point of contact where these can be gathered and posted and distributed.

DR. CONNOLLY: And then will you send all of those reports to all committee members; will you make a qualitative judgment or quantitative

judgment on quality?

DR. HUSTEN: If you just send random articles, we might look at it and say do we think it's relevant to the topic. If you're saying this is something I think the committee needs to rely on because of this or the other, we're going to give it --

DR. SAMET: Let me actually rephrase it. I don't think nor would I want FDA to be, let's say, a quality filter on what moves into the process. That can certainly be your approach to the white papers that you, Allison or somebody at the office exclude or include. I think if articles are to be considered by TPSAC as we write the report, these will be evaluated by TPSAC; I think just to be very clear about that, so.

DR. HUSTEN: Yes.

DR. SAMET: Yes.

DR. CONNOLLY: I'm sorry. Jon, on transparency, if TPSAC reviews, how are we going to assure transparency with the industry and with the public?

DR. SAMET: I think as each writing group takes on evaluation of evidence, they will need to state exactly how they have evaluated. Again, I don't think in the time frame that we're necessarily going to take 500 articles and do a table on each one, but I think, as I mentioned before, for those that are given particular emphasis or those that are not given emphasis, I think we'll need to state why.

DR. CONNOLLY: One last point, Jon. Do you see the committee or the subcommittee holding subsequent meetings where we then on our own invite experts in to testify on areas where we want more clarification if they're an expert in particular field?

DR. SAMET: I will possibly ask Karen to provide some guidance. I think if we want to have discussions -- I'm not sure I would use the word "testify" -- that that would need to be done between the subcommittee and those individuals in some public meeting, forum. We could certainly hold public meetings. The Web is useful format I

think to gather additional information.

DR. TEMPLETON-SOMERS: We can do that with the proper time allowed ahead of time for paperwork and possible SGE appointment or guest paperwork.

DR. SAMET: It won't be simple.

Other comments? So any further thoughts from the FDA?

DR. DEYTON: I don't really have anything in addition to add. I think your framing of the task here is spot on from what FDA's needs are. And I just echo what Corinne said. We're just delighted that the committee is moving towards the concept of developing some of standard framework for judging the weight of evidence. The better you do that, then the more you describe why that weighting, the description, will turn very important to us. Then when you hand FDA your report, that gives us a rich depth and breadth upon which to then understand what we might be able to do.

So personally, as you referred to, I've

struggled with these things in my years at Department of Veterans Affairs, that this committee this early is grappling with. This concept of framework and weight of evidence and how to have a standard is very important, and I think we all really appreciate you going down this path and support it.

DR. SAMET: Thanks. Corinne?

DR. HUSTEN: I just wanted to address one of the other questions that came up about postponing the report. I think the committee needs to understand you have lots of work to do and lots of other work besides this report. You have another report that'll be due the year after the menthol report on dissolvable tobacco products. You may be getting modified risk applications to review. We may have other topics that we want to bring to you. We've already brought the harmful and potentially harmful constituents.

So I think unless you want to quit your day job and move into an apartment a few blocks

from here, we need to ask you to use the data you have, write the report based on the data you have, make the recommendations based on the data you have. It doesn't mean that we can't continue to gather data and analyze it. It doesn't prohibit us from bringing this topic back to you if we feel we need to, but we need you to focus on doing as much as you can with what you have by March.

DR. SAMET: How do you get off TPSAC?

[Laughter.]

DR. SAMET: Let's see, the other --

DR. DEYTON: We do have you sort of in a locked compound here, so we could keep everybody for -- a lot of space here.

DR. SAMET: So just one other thing I think before we take a break. I also did provide that updating on the menthol subcommittee, and I just want to see if there's any questions about that just so we can sort of set aside the segment as we move on to the reports from the UCSF team about the document reviews.

So any questions? Remember I showed

those slides right at the start from the menthol subcommittee.

[No response.]

DR. SAMET: So I propose a 15-minute break, so exactly quarter of. And just as a reminder, committee members, no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. So back at 10:45.

(Whereupon, a recess was taken.)

DR. SAMET: Okay. We are back in session after a very generous break. We're going to move on now to the reports of the reviews of the Legacy documents. We're going to hear from Stacy Anderson first from the group at the University of California San Francisco. They've provided already some very extensive reviews of the evidence. Clearly, the documents are still in progress, but there's an awful lot of useful information in them.

Then our next presenter, Valerie Yerger, we're going to hear by DVD and then she's going to

be here. She has a personal commitment, but then should be here for questions.

So let's see how this goes around figuring out how lunch fits in.

So, Stacey, thank you and let me turn things to you.

Legacy Documents Presentation

DR. ANDERSON: Hi, I'm Dr. Stacey Anderson. I'm an assistant adjunct professor in the Social and Behavioral Studies Department at the University of California San Francisco. I'm also affiliated with UCSF Center for Tobacco Control Research and Education. I've been researching the publicly-available tobacco industry document archives since 2003. I'm one of an eight-person team at UCSF charged by the FDA with analyzing the internal industry documents to determine what the tobacco industry may know regarding a number of topics related to menthol.

The UCSF team produced six white papers that provide reviews of our findings. The three substantive presentations I will give today will

provide a general overview of some of these findings rather than a complete record of what's presented in our white papers. For this reason, the team asks you to refer to our white papers for the complete reviews.

Now, the authors of all papers being presented to the committee today followed the same basic research methodology. So rather than repeat that methodology on each presentation, I wanted to show you the basic methodology once and then fill in the specific details for each paper in the individual presentations. This brief presentation is an overview of the main elements of conducting tobacco documents research.

The Legacy Tobacco Documents Library or LTDL currently contains more than 11 million documents representing more than 60 million pages of information, created by the major tobacco companies related to their advertising, manufacturing, marketing, sales and scientific research activities. These documents were previously secret internal industry documents that

were made publicly available through litigation against the tobacco industry and are housed at the electronic library, the Legacy Tobacco Documents Library, found at the website that you see at the bottom of the page there.

The FDA staff requested a review of tobacco industry documents made available initially by a 1994 lawsuit brought by the state of Minnesota against the major tobacco companies in the United States. We conducted analyses of these documents in order to assess the knowledge and research conducted by tobacco companies on menthol in its relation to the following: marketing and consumer perceptions, initiation, smoking topography, nicotine dependence, potential health effects and smoking cessation.

Research questions were provided by the FDA and in some cases refined by the researchers ourselves to reflect the findings from specific analyses of the documents. Our charge was to answer the questions posed by the FDA staff according to what was found in the industry

documents. The FDA staff had no participation in the conduction of this research nor in the creation of the papers, all or in part. By necessity, what will be presented today is only a piece of the larger puzzle.

The broad research questions one begins with guide initial searches of the documents collections. One generates a list of search terms likely to return documents relevant to the research questions, and from qualitative analyses of those documents, the researchers refines research questions and continues the iterative process of searching, analyzing and refining as a coherent story emerges.

The LTDL search page allows for a basic search with one simple search box, an advanced search, which is the screenshot you see here, and an expert search involving the use of special LTDL codes. One has the option of searching different elements of the document such as document type, for example, a report or an advertisement; persons named or the default that you see here highlighted

in blue, the entire record among the others that you see.

One also has the option of searching all the collections shown by all of the boxes checked at the bottom housed at the LTDL, for instance, if one wanted to only search the thousands of pages of the Brown & Williamson Tobacco Corporation documents that were donated unsolicited to the UCSF Tobacco Control Archives back in 1994. Also available is the ability to limit the date of the documents searched for in addition to the other elements that you see on this page.

In the example shown here, I've used three search terms, "menthol, marketing and African-American," from the example that I showed you on the previous slide without specifying any other parameters. Here is the first of 440 pages of results returned, totaling 4,392 documents that include those search terms. You see where in the record and also an excerpt in the document text, which is highlighted in yellow -- where each of these search terms appears. Clicking on the top

link of each record will send you to the searchable PDF of the document.

I want you to look at the portion of the reference down at the bottom, and part of that is boxed in a red box. This part in the red box is a series of alphanumeric characters. That represents the TID corresponding to this document. The TID is a unique code assigned to individual documents in the archives, and only one document will be referenced by its specific TID. So the TID is an efficient way to cite a specific document.

The researchers build on a relevant collection of documents by reading and analyzing the search results and by conducting snowball searches based on the contents of the documents returned in initial searches. For instance, specific brand names may be mentioned in this document that you see here that are important to understanding the research question or the author and/or recipients of the documents may be involved in research projects relevant to the research

question. Gaining this additional information through qualitative analysis of the documents allows the researcher to refine the research questions and fill out the analysis with more targeted documents data.

These interpretive methods employed in this research, which is also used by historians and social scientists who study archival and documentary data, involves iteratively reviewing data to construct an account that is coherent, supported by the evidence, and deeply contextualized.

Now, on the last slide I pointed out duplicate titles. The results that are returned in the LTDL include many multiple copies of many documents, so the researcher must decide which irrelevant and duplicate documents to exclude from a search. Relevance was based in this case upon electronically searching or reading a document and deciding if it included content related to the topic of the specific research questions presented by the FDA staff.

Tobacco companies investigated issues in order to increase their market size rather than to understand public health issues, thus many of the tens of thousands of returned documents did not appear to be directly relevant to our questions. The process of analyzing documents for relevance to the study and representativeness of the study findings is this: Initial search terms yielded often tens of thousands of results, sometimes hundreds of thousands of results. So due to time and resource constraints, for each set of results, the researchers reviewed the first 50 to 300 documents returned.

Based on an initial screen, documents that did not appear to be relevant to the research questions and duplicate documents were thrown out. Documents that passed this screening and were determined to be worthy of further review were read and analyzed. And through qualitative analysis and contextualization of these, the researchers found specific themes emerging. Based upon these thematic findings, the researchers

selected the documents that most accurately summarized the research findings to cite in the papers. Thus, it is the findings based upon the analysis of the tobacco companies own statements that determines the selection of representative documents to be cited.

Not cited were documents that summarized the thematic findings but perhaps not as eloquently, those that supported the findings but were difficult to understand if out of context or were deemed not relevant to the research questions after our further reviews.

Qualitative documents research has some limitations. First, the sheer quantity of available documents -- and I said over 60 million pages -- forces researchers to make decisions about which search terms retrieve the most relevant material, and establishing a comprehensive list of search terms capable of returning every document relevant to a topic is simply not possible.

Further, the LTDL is frequently updated

as tobacco companies provide additional information and documents become available through subsequent litigation. Therefore, some relevant data in the archives will not have been included in the analyses.

Second, alternate phrasing, code words and acronyms are sometimes used by tobacco industry executives. For example, in a 1974 British American Tobacco memo about a visit to a toxicology consulting firm, it was noted that, quote, “Reference to menthol should be omitted from such documents and which should refer generally to toxicity studies,” end quote. Brown & Williamson used code terms when referring to menthol. Acronyms were also commonly used, which are often unclear if the context is not known.

Finally, specific to these white papers, in analyzing the documents in a limited time frame, context may have been lost, and therefore, these white papers cannot be a comprehensive report of all the documents related to menthol. Understanding the time period when a document was

written, who wrote a document, why a document was written, or why a study was performed requires time for reviewing and linking documents together. It is also difficult to compare statistics gathered using different methodologies used by numerous companies over several decades.

So there you have the Reader's Digest version of tobacco documents research. This section of the presentation will cover documents research on the marketing of menthol cigarettes and consumers' perceptions of menthol.

The FDA asked four questions on the subject of marketing menthol cigarettes and the perceptions that consumers have about menthol. First, are or were menthol cigarettes marketed with health reassurance messages? Did the messages convey menthol cigarettes were safer or less harmful than full flavor or non-menthol cigarettes? Second, what other messages come from menthol cigarettes advertising? Third, how did smokers tend to view menthol cigarettes? Did smokers view menthol cigarettes as safer or less

harmful than full flavored cigarettes or non-menthol cigarettes, and did this cause brand switching among smokers? And fourth, were menthol cigarettes marketed to specific populations; how marketing practices led to an increase in menthol use among youth or various U.S. subpopulations?

You're now familiar with the basics of tobacco documents research methods. For the white paper corresponding to this section of the presentation, I began my initial searches with the initial search terms that you see there. This initial set of keywords resulted in the development of further search terms and combinations of keywords such as menthol cigarette brand names, project names, individuals and companies named in correspondences and on research reports, and specific target groups.

Relevant documents were found in the following subject areas: One, marketing menthol using health reassurance messages; two, user imagery focused marketing; three, consumer perceptions of menthol products; and four,

targeting specific populations with marketing campaigns.

I screened nearly 7,000 documents for their relevancy and duplication of which nearly 1,000 I believed to be worthy of further review. A subset of 81 of those documents, which were found to be relevant to the research questions, posed for this topic were cited in the final white paper. I will share some of those references in this portion of the presentation.

From the beginning, menthol cigarettes were popularized as a remedy to the burn, dryness and throat irritation that accompanies smoking. Menthol brands were all sold on this general platform when menthol was first to introduced to market, but I’m using just one representative example per point in the interest of time here today.

In 1933, Brown & Williamson’s KOOL menthol brand was introduced as a product for occasional use that would promote throat comfort. The underlines that you see there are slogans from

early KOOL ad campaigns claiming that your throat will never get dry and positioning the brand as a remedy to smoker's hack. The ad on your left side of the screen is from 1943, for KOOL, presenting the brand as the solution to raw sore throat when a smoker has a cold.

In a 1964 brand evaluation, Brown & Williamson noted that, "Emphases on the throat with its important health implications has been an important part of KOOL advertising since 1960. In light of the smoking climate in recent years, this could very well have benefited the brand," the smoking climate being an increase in public awareness of and concern over the health hazards of smoking.

A review of KOOL advertisements from 1933 to 1980 conducted by Cunningham & Walsh for Brown & Williamson revealed that they knew smokers perceived menthol as less harmful, which benefited the KOOL brand. And we see that the explicit intention was to encourage perceptions of product safety and to plant the brand in the health

reassurance segment.

With the introduction of R.J. Reynolds Salem brand in 1956, the ostensible health benefit of menthol was overtaken by the taste benefit of menthol, and the style moved from the occasional use into the regular use arena. This is summarized nicely in a 1982 menthol marketing presentation by Brown & Williamson. “Salem created a whole new meaning for menthol. From the heritage of solving the negative problem of smoking, menthol almost instantly becomes a positive smoking sensation.”

Menthol in the filter form in Salem advertising was a “refreshing taste experience.” Undoubtedly, the medicinal menthol connotation carried forward in a therapeutic fashion but as a positive taste benefit. Menthol was positioned as a cigarette for all occasions, which, of course, means larger sales volume than if it had remained a product for occasional use only. This ad on the right side of the screen is a Salem ad from 1957, which uses some form of the words “fresh” or

"refresh" no fewer than seven times on a single page.

Perhaps most commonly, menthol is thought of as an African-American cigarette style, and to an extent, the evidence from industry documents supports this perception. The evidence is clear, however, that tobacco companies did not intend for menthol to be only or even mostly an African-American style but rather a style that's strongly associated with group identity for many different subgroups in the market, including but not exclusively African-Americans.

As one example of linking menthol to African-American identity, Diane Burroughs of the R.J. Reynolds marketing development department stated in 1984, "Younger adult blacks of the 1930s to 1950s had basically gone with whatever brand was big among younger adult white smokers. In the 1960s, they began to coalesce behind KOOL, which had only a 2 percent share among younger adult whites. It was time for blacks to build their own brand in the 1960s, the heyday of the Martin

Luther King and the Black Pride." The ad you see here is likely from the 1970s, but Brown & Williamson aggressively promoted KOOL back in black publications such as Ebony since at least 1962.

Lorillard's Newport brand, the brand with the youngest demographic in the market, is a prime example of messages of fun, sociability and youth in menthol marketing. Philip Morris observed in 1995 that "Newport's consistent theme, Alive With Pleasure, and strategy, Friends Having Fun, have given Newport a clear identity in smoker's minds, that Newport was the only brand to capitalize on important sociability aspects of the category."

The ad that you see here is one that Philip Morris included in this analysis of Newport's Friends Having Fun campaigns. Although youthfulness and sociability are not images restricted to menthol users, these user images appear to carry certain weight within the menthol market. R.J. Reynolds observed in 1981 that, "The benefit of smoking, which has most frequently and

most successfully been exploited by brand families, appears to be social interaction. For example, some brands, such as Newport, have focused on the younger adult peer group aspect of social interaction."

Batten, Barton, Durstine & Osborn, Incorporated -- focus group interviewees conducted in New York and Minneapolis on Tennyson cigarettes, "Menthol smokers do view menthol cigarettes as safer." This focus group conducted for American Tobacco in 1969 tested in part perceptions of a new menthol product. It was observed that there were indications that menthol smokers subconsciously perceived that menthol cigarettes as being healthier. There was somewhat of a health image associated with menthol related to its masking of the tobacco taste and its association with medicine, colds and sore throats.

In 1978, Brown & Williamson explicitly noted the strength of its KOOL franchise, noting that it rides on the connotation that menthol has health overtones and that the KOOL Super Lights

extensions menthol and tar delivery has synergistic therapeutic implications. And in 1980, Brown & Williamson heard comments from interviewees that they began smoking menthol cigarettes when they had a cold and that menthol cigarettes are better for you.

These beliefs about the relative healthiness of menthol caused brand switching. Lorillard observed in 1972 that, “Brand switching has resulted in 13 percent gain for menthols, which is larger than the 8 percent gain for Hi Fi brands,” meaning high filtration brands, the only types gaining from switching; and cited research participants’ explanation that, “I started smoking KOOLs when I had a cold. It felt good, so I kept on smoking them.”

This problem of colds and sore throats is ubiquitous in documents discussing consumer perceptions of menthol cigarettes as safer or less harmful than regular cigarettes. Menthol cigarettes were marketed to specific populations, including African-Americans, young people, women

and Asians, and this contributed to the popularity of menthol styles in these groups.

In 1991, the shareholders of Loews, then parent company of Lorillard, wrote to the company, observing that “80 percent of Loews’ ad dollars go for Newport. From July to September in 1986, 4.7 million of the 6.5 million spent on advertising went to billboards.” The shareholders wrote, “Studies show that the poorest neighborhoods, the ones where most billboards are placed, had the highest incidence of health-related problems associated with tobacco, and more black males than white males percentage-wise, and more black females than white females percentage-wise smoke.”

A 1983 cigarette ad study among low income black smokers for Newport revealed, “The use of menthol cigarettes among the 18 to 34 lower income black segment is almost universal. Nearly nine out of ten smokers currently smoke a menthol brand.” Noting changes from data in 1979. The study observed that, “Overall, black smokers have a better recall for advertising for specific

brands than in 1979."

Menthol styles are often lumped together by tobacco marketers in marketing language such as R.J. Reynolds' coolness segment used to identify the menthol market. Consumers in this segment are the youngest, most economically disadvantaged and the most likely to be in minority and ethnic groups. R.J. Reynolds noted that, "Coolness segment smokers tend more than average to desire their brand of cigarettes to symbol personal qualities such as youth, modern womanhood, romance, career orientation and success."

A 1985 study for Brown & Williamson on menthol in Japan showed that, generally speaking, menthol cigarettes were perceived to be lighter than ordinary cigarettes. As a result, they were perceived to be consumed primarily by women, especially younger women, followed by other beginning smokers. The study report advised that, "These aspects should be seriously considered by a marketer of menthol cigarettes, since the primary target segment is young women, such as female

students and office girls."

To sum up, in answer to Question 1, menthol cigarettes were originally marketed on a health platform and health messages successfully convinced consumers that menthol cigarettes were better for them than non-menthol cigarettes.

In answer to Question 2, other messages in menthol cigarettes advertising included refreshing, fresh, cool and clean, identity and in-group belonging and fun-loving, sociable and youthful.

In answer to Question 3, smokers tend to view menthol cigarettes as safer or less harmful than full flavor or non menthol cigarettes, and this contributed to brand switching among some smokers.

Finally, in answer to Question 4, menthol cigarettes were marketed to specific populations, including African-Americans, young people, women and Asians, and this contribute to popularity of menthol in these groups.

Here are the references for this

presentation, which are in your packet.

Now, this segment of the presentation will deal on menthol cigarettes and the initiation of smoking. I should point out that this paper was written by Kim Klausner in the UCSF library and the documents searching was prepared by Rachel Taketa, also in the library, and I'm presenting their work today.

The research questions were, does menthol make it easier for young or new smokers to start smoking? Do menthol smokers start smoking earlier than non-menthol smokers? Is there higher use among youth who have been smoking for less than a year? Three, did current non-menthol smokers start smoking menthols before switching? Four, does menthol accelerate the progression to establish smoking?

As a result of initial searching, two other questions were added to these. Did the tobacco industry market menthols to youth? And if so, what images did it use? And to what extent do non-menthol smokers smoke menthols?

The LTDL was searched using the phrases that you see there in the initial search bullet point. Over 2500 documents were screened for their relevancy and duplication, of which just over 100 were believed to be worthy of further review. A subset of 49 of those documents, which were found to be relevant to the research questions posed for the topic, were cited in their white paper. I'll share some of those references in this presentation.

In answer to the first question, does menthol make is easier for young or new people or inexperienced smokers to start smoking, analyses of documents suggest that the market research on menthol began in earnest in 1970s. Tobacco companies found that sensation or taste plays a large role in new smokers' decision to smoke menthols. Menthols are easier to inhale than regular cigarettes. They are less harsh and perceived to be soothing to the throat. Menthol smokers prefer a taste or effect that they experience as cool, refreshing and milder.

An R.J. Reynolds memo validated the common perception that it takes effort to acclimatize oneself to inhaling smoke. A low level of menthol eases this discomfort. R.J. Reynolds found that younger adults and young adults like menthol because of their mildness and smooth cooling sensation. They noted that, “Because of its relative mildness, several respondents report that they can smoke a mentholated cigarette first thing in the morning, whereas doing this with a non-mentholated cigarette produces unpleasant results.”

In addition to sensation, taste or effect, though, the companies found that there were social factors that propelled young people to smoke menthols. Young people under age 18 have a harder time purchasing cigarettes and are more likely to share cigarettes obtained from older people among their friends. If their family or friends smoke menthols, then this is the type of cigarettes more easily available to them.

But older siblings and friends are not

just a point of access for menthol cigarettes. Adolescents want to emulate them in order to appear cool or with it. A 1978 Lorillard study of African-American smokers reported peer and family influence as prime factors in their first brand selection.

This 1982 British American Tobacco Company report notes that, “Smoking menthols functions also as a guilt reducing mechanism. Since it successfully alters the total smoking experience, providing its own kind of filter, it manages in some small measure to subtly disguise the sin. Some smokers go further ascribing medicinal properties to the mentholation.” The same report also says that, “Some people choose menthols because they perceive them to be less intrusive or even less harmful than regular cigarettes.”

A Brown & Williamson document states from 1987 that, “Menthol brands have been said to be a good starter product because new smokers appear to know that menthol covers up some of the tobacco

taste, and they already know what menthol tastes like, vis-à-vis candy. The level of menthol in products is, however, critical. A product having a moderate to high menthol taste will usually be rejected by starters, while the same level will be quite acceptable to established menthol smokers."

An R.J. Reynolds' analysis also confirmed this phenomenon. "Once a smoker adapts to smoking a menthol product, the desire for menthol increases over time. A brand which has a strategy of maximizing franchise acceptance will invariably increase its menthol level. Thus, once a brand becomes successful, its product will evolve in some manner that is not optimal for younger adult, non-menthol smokers or switchers."

So do menthol smokers start smoking earlier than non-menthol smokers? No evidence was found that shows menthol smokers start earlier than non-menthol smokers or that address the type of cigarettes smoked in the first year of smoking. There were only data on the types smoked in the past year without knowing whether it was the first

year a person started smoking.

Analyses of documents suggest that beginning youth smokers, those who may not have purchased packs on their own, smoke cigarettes that are available to them, those acquired by older friends or family members. While they may prefer a brand or type, they may smoke what they can get. It may take some time before a smoker confirms a preference by either refusing to smoke certain brands or types or by buying their own. Once this happens, though, young people switch brands or types more frequently than older smokers do. Sometimes menthol smokers under age 25 switch to non-menthol brands, but more often, it seems non-menthol smokers switch to menthol.

Companies were usually more interested in researching about brand loyalty than about type loyalty, but these studies provide some evidence about switching. There is ample evidence, however, that shows menthol smokers had smoked non-menthols whether as confirmed purchasers or in the initial stages of trying several brands.

There is no way, though, to determine precisely what proportion of menthol smokers started out smoking non-menthols, and this figure would have undoubtedly changed over time.

Analyses of documents show that menthol smokers in general like the taste and that they were more apt to switch to another menthol brand than to a non-menthol brand if they were dissatisfied with their smoking experience.

This 1976 R.J. Reynolds report shows that younger smokers started with the popular brands and then moved to menthol for a variety of reasons, the rejection of tobacco taste, the search for milder cigarettes, personal influences or the circumstances of having a cold and wanting to continue smoking, but being unable to handle the hot taste of cigarettes in an already irritated throat.

This Imperial Tobacco Company document points to similar reasons for switching from a non-menthol to a menthol but goes further in saying, “Once having made the commitment, however,

it seems to be an unusually strong one. Even when they try, as sometimes they do, they typically are not able to revert to a non-menthol brand."

A 1984 Philip Morris study with a sample size of over 26,000 people noted that, "There was some movement from menthol to non-menthol, but that larger percentages of smokers who switch to a menthol came from a non-menthol than vice versa."

The fourth question was, does menthol accelerate progression to established smoking? They found no evidence that indicated that people who start smoking menthols rather than non-menthols moved more quickly to becoming regular daily smokers. However, analyses of the documents showed that industry-collected demographic data on age, gender and race, among other factors, on beginning menthol smokers because it fully expected young menthol smokers to remain tobacco consumers.

This memo notes peer influence or the propensity towards conformity among smokers under age 18 and says, "Menthols in general do better

among the very young and among very young blacks. Almost the entire market is accounted for KOOL, Salem and Newport." This 1984 R.J. Reynolds study also shows that, "Newport's fundamental growth has been due to younger adult blacks." And this 1985 R.J. Reynolds study reports, "High menthol use among African-Americans," but also points to disproportionate use of menthol by women aged 18 to 20.

Analyses of documents shows that companies with menthol brands decided to market their entries to young people once they saw this type of cigarettes appealed to youth. These campaigns were based on the assumption that peer influence largely drove youth smoking choices. There was a self-reinforcing success loop that could be achieved with this approach, market to youth with youth-oriented images, causing sales to young adults to increase, which gives rise to the perception that these brands are popular, which attracts more youth smokers and encourages a company to expand the marketing efforts toward

youth. Each company knew the importance of marketing to African-American youth and did so.

In an analysis of Newport's rising market share, which was affecting sales of Salem and KOOL, R.J. Reynolds noted that, "Newport is placing increased emphasis on both young female and young male publications and reducing older female publications. Its image is young, no major negatives. The brand's advertising talks directly to young people, situations, attitudes. Newport's promotional plan tends to be directed toward its young smokers with youth-oriented premiums, including pack purchases."

Lorillard itself noted that, "Newport image appears to be far more malleable and promising in terms of its appeal to younger menthol smokers, such as those who participated in this specific study." Newport is generally associated with younger smokers, both men and women, with both blacks and whites by the respondents who participated in their study. And it wasn't until the 1980s, though, that Reynolds

started marketing specifically to youth. By 1984, they were reinforcing Salem's product and user imagery to younger adult smokers by focusing positioning and advertising on younger adult smokers, improving the appeal of the Salem Spirit campaign and utilizing widespread, high visibility market presence through out of home and point of sale.

R.J. Reynolds emphasizes the importance of the younger adult African-American market to menthol sales. Despite evidence that Lorillard did market heavily to younger African-Americans, they indicate here that those campaigns also ran in white communities. And here you see two examples of youth-oriented advertising.

Analyses of documents suggest that non-menthol category of smokers is porous; that is, some non-menthol smokers occasionally use menthol cigarettes either for a change of pace or because of throat irritations or cold or when they bum cigarettes from someone else. Estimates of the frequency of this phenomenon of the volume of

cigarettes involved vary from company to company and vary over time. If these non-menthol smokers are not counted as menthol smokers, then the number of menthol smokers would be underreported in health surveys.

Analyses of the documents suggest that some youth start smoking menthol cigarettes when they begin tobacco use or within the first few years of smoking. They do this for a variety of reasons, but according to the publicly-available tobacco industry documents, the main ones are, one, the relative ease of smoking menthol cigarettes for the uninitiated smoker and, two, its availability from family and friends.

Secondarily, some youth smoke menthols because they perceive them to be less harmful than non-menthol cigarettes. The tobacco industry has encouraged this idea through advertising, which we've just seen. This perception may be fueled by the fact that some youth use menthols for the first time when they have a sore throat or a cold or because they feel menthol to be less irritating

than non-menthol.

There's much switching of brands and types of cigarettes in the youth and young adult markets both from menthol to non-menthol and vice versa. Based on the documents found for this study, though, once smokers have chosen to be menthol smokers, there is very little switching back to a non-menthol brand. Rather, the longer someone smokes menthols, the more they desire a stronger menthol taste and they will tend to switch to a menthol brand with a higher concentration of menthol in the tobacco. The tobacco industry understands this and specifically keeps some brands at a lower menthol tobacco ratio in order to attract more novice smokers, even at the cost of losing them as they age.

The tobacco industry tracked race and sex in their analyses of the youth and young adult market. They knew that young African-American smokers smoked menthols at higher rates than other ethnic and racial groups and that young, women regardless of race, smoked menthol more than young

men. The tobacco industry, eager to attract those young smokers, designed marketing campaigns that they hoped would appeal to those segments. And the references here are also included in your packet.

The last segment of this presentation will cover documents research on menthol and its relation to smoking cessation behavior. The FDA asked two questions on the subject of menthol cigarettes and their potential relation to smoking cessation behavior. First, compared to non-menthol smokers, do menthol smokers have a harder time quitting, report more or fewer quit attempts and/or have higher or lower quit rates? And second, compared to non-menthol smokers, are menthol smokers more or less likely to relapse or delay quitting and/or to experience different odds of maintaining abstinence long term?

Regarding the potential direct role of menthol and quitting, quit rates and relapse, it appears that most of the information tobacco companies considered came from the biomedical

literature and not from studies carried out by the companies in-house. They seemed to have conducted very little research on their own on these exact questions.

A review of the internal industry documents, however, shows that there was considerably more interest in menthol's indirect role in keeping smoking attractive enough to dissuade cessation. Given that, I refined the research questions to reflect the tobacco industry's apparent interest in these indirect mechanisms and their potential impact on cessation. Important areas to focus on to better understand the industry's interest in the indirect role of smoking cessation were identified as follows: first, perceived sensory and taste rewards of menthol in potential relation to quitting; second, motivation or desire to quit among menthol users, including health concerns and social unacceptability of smoking; and third, sociodemographic correlates of both menthol usage and cessation patterns.

The initial search terms for searching the LTDL are those you see at the top of the screen there. This initial set of keywords resulted in the development of further search terms and combinations of keywords, including menthol cigarette brand names such as Newport, identified demographic groups such as African-Americans or women, psychographic segmentation reports such as R.J. Reynolds' coolness segment, identified motivations such as sensation, project names such as Project GS, and individuals and companies named in correspondences or research reports such as A. Udow from Philip Morris.

Relevant documents were found in the following subject areas: perceived sensory and taste rewards, motivation or desire to quit and sociodemographic correlates. I screened nearly 5,000 documents for relevance and duplication of which just over 500 I believed to be worthy of further review. A subset of 60 of those documents, which were found to be relevant to the research question posed for this topic, was cited

in the corresponding white paper. I'll share some of those references in this presentation.

Menthol smokers perceived pleasant or minty or a medicinal-like taste and soothing, cooling and anesthetic sensations with menthol cigarettes. These perceptions appear to discourage quitting in menthol smokers.

A 1990 Booz Allen & Hamilton report, strategizing for R.J. Reynolds in the face of threats to the industry volume, suggests the role of menthol. This report emphasizes that the original reason for menthol was therapeutic, providing a refreshing alternative to hot, harsh tobacco taste of existing brands, and that a cigarette product should provide a smooth smoking experience that is easy to adapt to.

Menthol acts as a means of masking, covering up or avoiding the negatives of smoking, particularly the heat, harshness and dryness of cigarette smoke. R.J. Reynolds observed in 1980 that, "Menthol smokers want to smoke a refreshing cigarette. They smoke menthol cigarettes

primarily to avoid the negatives associated with non-menthol smoking, i.e., harshness, dryness, hot taste, unpleasant aftertaste. The indirect route to this end is noted. Menthol is not a major benefit in itself but is a means to achieve coolness, smoothness, mildness and a clean taste."

Even among menthol users that recognize the negatives associated with smoking, menthol is perceived to be something of a solution to the negatives and as an alternative to quitting. This was explicitly acknowledged in the 1973 study of the attitudes and behaviors of menthol smokers conducted for R.J. Reynolds. Generally, when a respondent reported that he made a conscious decision to switch to a mentholated brand, it was because of some problem, minor or major. For instance, many switched to mentholated cigarettes because of throat irritations, colds, coughs or chronic bronchitis. Some respondents saw smoking a mentholated brand as the only alternative to giving up smoking altogether. Perhaps not surprisingly then, a 1979 Roper Organization study

of smokers' habits and attitudes found that menthol smokers expressed slightly less desire to quit smoking than do non-menthol smokers. Thirty-nine percent would like to quit versus 43 percent of non-menthol smokers.

One main motivation for smokers to quit is health concerns. Menthol's cooling, soothing and anesthetic effects mask superficial health effects such as throat irritation and cough in menthol smokers, which lessen their concern about health effects. Menthol's ability to mask the pain and burn of smoking and its perception as a milder and therefore safer product as compared to regular cigarettes has caused some smokers experiencing pain and discomfort to switch from non-menthol to menthol brands and styles, particularly among young people who start with popular youth brands.

For instance, the Sherman Group conducted a reconnaissance study of Newport for R.J. Reynolds in 1976 and found, "In rejecting the regular cigarette taste, the smokers are referring

back to their own experiences. These young smokers began smoking the popular brands and moved to menthol for a variety of reasons or circumstances."

Now, we've seen this before, the rejection of tobacco taste, the search for a milder cigarette, having a cold and wanting to continue smoking but not being able to handle the hot taste of cigarettes in an already irritated throat.

This is viewed as a potential opportunity for tobacco companies. The Landis Group reported to Philip Morris in 1992 that, "Over half of the people interviewed were non-menthol smokers first and changed to menthol for a variety of reasons such as during an illness, the non-menthol was too harsh. In view of these findings, it appears that there may be an opportunity to convert non-menthol smokers to menthol cigarettes."

I should point out this stands in direct contrast to having them convert from non-menthol smokers to nonsmokers.

An undated report by Brown & Williamson on lapsed and quitting smokers noted that, “Health-related reasons are by far the most prevalent reasons to quit,” and observed that, “The reasons for consumers’ awareness of less strong cigarette brands, including Salem and Newport, were taste, flavor, tar and nicolene (ph)” -- which I’ve tried to determine if that’s a typo or not and I was unsuccessful. But I think they mean nicotine. I can’t confirm that -- “and throat related.” This report found an increase in concern about health issues but a decline in desire to give up.

The Creative Research Group perhaps described the soothing qualities of menthol in its potential role in discouraging concerned smokers from quitting most plainly in a 1986 report for Imperial Tobacco. The report stated, “Quitters may be discouraged from quitting or at least kept in the market longer by either of two product opportunities. A less irritating cigarette is one of those. Indeed, the practice of switching to

lower tar cigarettes and sometimes menthol in the quitting process tacitly recognizes this. The safe cigarette would have wide appeal, limited mainly by the social pressures to quit. Unsuccessful quitters are motivated disproportionately by physical reactions and social forces to stop smoking, but health remains the most often specified reason."

These statements explicitly recognize menthol's ability to soothe irritation as a barrier to quitting and acknowledge the lack of quitting success in people who claim physical reactions like an irritated throat as their primary motivation for quitting.

Another main motivation for smokers to quit is the social unacceptability of smoking. Menthol smokers believe menthol to smell better and to be less offensive to others, which lessens menthol smokers' sense of the social unacceptability of smoking.

Addressing social acceptability concerns, R.J. Reynolds noted in a 1990 brand positioning

report that, “For the Salem and Newport brands, menthol served to lower the risk of offending others with odor and smoke and that Salem smokers in particular endorse the following questionnaire items: ‘I’m imposing, my clothes smell bad, I want a less offensive cigarette, people object, et cetera.’”

The report observed that, “Another potential example of recent success among menthol brands may be Horizon. Horizon is not a menthol-based proposition. It is positioned much more broadly to address social concerns about smoking, yet 40 percent of its franchised in test markets smoke the menthol styles. Menthol may support Horizon’s positioning as a brand with a solution to social concerns.”

Now, R.J. Reynolds’ brand Horizon was first introduced as Chelsea and was not advertised as a menthol product but rather explicitly as a cigarette with a pleasant aroma from the lit end but was rejected because mentioning odor only served to emphasize the problem.

The 1991 report of focus group testing of Horizon for R.J. Reynolds revealed that, “Telling smokers that Horizon will make them and/or their surroundings smell better implies that they currently smell unpleasant or offensive. Smokers may privately acknowledge and even openly admit this but may prefer not to smoke a cigarette that blatantly brands itself as a solution to an odor problem. Conversely, menthol not advertised overtly as a solution to malodorous cigarette smoke appears to be more readily embraced by menthol smokers who express cosmetic concerns such as odor as more socially acceptable to be around relative to non-mentholated smoke.”

As the Roper Organization’s 1979 report on smokers’ habits pointed out, “Menthol smokers are slightly less inclined than non-menthol smokers to feel uncomfortable about smoking around others.”

Menthol appeals to some sociodemographic groups who are also known to have difficulty in initiating quitting or staying quit, including

women, low income smokers and African-Americans. It appears that tobacco companies took an interest in this overlap between sociodemographics, menthol use and quitting.

For instance, Philip Morris' Myron Johnston wrote in 1981 of his suspicion that, "Demographic and socioeconomic variables were confounding the relationship between tar and nicotine deliveries and average daily consumption." The demographic and socioeconomic variables he examined match closely the menthol market sociodemographics as he observed.

In many cases, the demographic variables provide better predictors of cigarette consumption than tar and nicotine. This was particularly true of blacks among whom the socioeconomic characteristics were best predictors in seven of the ten cases that he ran in statistical tests, and income the best predictor in four of those cases.

Similar, as R.E. Thornton of British American Tobacco observed in his 1976 study of the

smoking behavior of British women, “There is some evidence that women are more highly motivated to smoke than men and find it harder to quit smoking.”

In terms of brands which are not specifically aimed at women, the following statement about women’s reactions to new concepts is best attributed to J. Bowling, group vice president of Philip Morris. “The ladies have led every major cigarette trend in the past 15 years. Our studies show that they were the first to embrace king-sized cigarettes, menthol, charcoal and recessed filters.”

Some data show that young people quit more than older people, older more established smokers do. However, the key brands that contradict this trend are two of the three most popular stand-alone menthol brands. A Philip Morris summary of their study of quitting compiled in 1988 showed that Newport was the only younger brand underrepresented among successful quitters. KOOL, like Newport, was also underrepresented

among successful quitters.

A 1978 study of ex-smokers, Philip Morris' F.J. Ryan said of age and quitting, "The most recent quitters, those who quit within one to three months, appear to be younger than those who quit some time ago. However, scanning the age at time of quitting data for those who quit a year or more ago, it's difficult to interpret the recent numbers in terms of a trend. We think it more likely that the initial quit rate for younger smokers is about the same from year to year but that their long-term success rate is poorer than the success rate for older smokers."

In other words, Ryan surmised that although menthol quitters were younger than non-menthol quitters, these younger quitters were more likely to relapse and not experience long-term abstinent success.

Although it's not clear why there is substantial overlap between the overall menthol profile of younger, nonwhite, female and low income and the sociodemographic variables that

predict difficulty in quitting or staying quit, it does seem clear from the internal industry documents that tobacco companies took an interest in this overlap.

So to sum up, in answer to the revised questions, how does menthol relate to sensation, taste and cessation, menthol smokers perceive pleasantly minty or medicinal-like tastes and cooling, soothing, anesthetic sensations with menthol cigarettes. These perceptions discourage quitting in menthol smokers.

How does menthol relate to motivation or desire to quit among menthol users? Two main motivations for smokers to quit are health concerns and social unacceptability of smoking. With respect to health concerns, menthol’s cooling, soothing and anesthetic effects mask superficial health effects, such as throat irritation and cough in menthol smokers, which lessen their concerns about health.

With respect to the social unacceptability of smoking, menthol smokers also

believe menthol smoke to smell better and be less offensive to others, which lessens menthol smokers' sense of the social unacceptability of smoking. These aspects of menthol that lessen concern for health and social unacceptability discourage motivation or desire to quit among menthol smokers.

How does menthol relate to sociodemographic correlates of both menthol usage and cessation patterns? Menthol appeals to some sociodemographic groups who are known also to have difficulty initiating quitting or staying quit, including women, lower-income smokers and African-Americans. And as I said before, although it's not clear why this overlap exists, it is clear that the tobacco industry executives took an interest in that overlap.

So, from an analysis of the internal industry documents, menthol's flavor sensation and perceived social acceptability attracts groups who have a hard time quitting and demotivate quitting in smokers who may otherwise quit.

Here are the references relevant to this presentation. You'll see those in your packet, and now it's time for clarifying questions.

Clarifying Questions

DR. SAMET: Okay. Thank you very much, Stacey. It's a remarkable amount of information that you've put together.

I'm going to suggest two things -- I see hands up -- that we not focus on any particular detail of the presentations. I think there was too much there, and I think we could be bogged down in discussion quickly.

I do think, from my perspective, there's a couple of issues that I think we'll have to think about as we look at this. One is that the reviews cover a long time frame, and I think we have to think very carefully about the relevance of some of what we heard to our current task. I mean, I understand there's an important historical perspective here on how we ended up where we are. So I think we need to think about that.

Second, the documents I think represent

an interesting form of evidence and one where the reviews take their own form, and as you begin to tell a story using your snowball approach, you sort of end up in places. And I think the committee will have to think about how it incorporates this kind of evidence, and as we look at it, whether we need to return to some of these sources ourselves and how we approach it.

So I think what we should do is maybe take the next 10, 15 minutes before lunch and ask questions I think in sort of the spirit of where we ought to be in our questioning or at the more general level.

So let's see. John, I think you were the first out of the block here.

DR. LAUTERBACH: Dr. Samet, I have clarifying questions to Dr. Anderson.

By the way, Dr. Anderson, I'm a frequent user of your website. I was even on it about 2:00 this morning. But what I noticed were that your documents, I think the most current date you had was 1992; yet, over the past week, I've pulled

documents from your website, I think even some at 2010. So I ask the question of how come we do not see any documents of a more recent time?

DR. ANDERSON: As I stated in the introduction to methods, there are 11 million documents plus, and in our time frame, we analyzed every bit that we could. And given what we deemed worthy of review, we analyzed those and determined the themes that came up. Given those themes, we selected the documents for our presentations that would be the most concise and the most eloquently stated representations of those themes.

In some cases, those documents are quite old. In some cases, those documents are more recent. Certainly, there are documents both old and very recent which are relevant to these questions that I simply cannot put in a white paper unless you read 5,000 pages of my writing or sit here for 15 hours listening to me speak on every relevant document.

DR. SAMET: So I think one question -- I think actually John’s comment sort of relates to

my more general question about sort of the relevance and the historical time frame. So I think these reviews will be useful, and I think as we discuss them more generally, I think after we hear the next set, we should ask this question of whether we would want some shaping of these reviews to have more intensity on one or another time frame. And I think that's just something that we should discuss, and I think that's raised by your presentation, this question.

Dan?

DR. HECK: Dr. Anderson, there was a lot of information presented here. Did you get a sense in your review of these documents -- we've seen, as the chairman has mentioned, some dramatic changes in advertising, marketing with the Master Settlement Agreement and such over the recent years, and certainly now with the advent of the FDA regulation.

Did you get a sense in your review that any of the practices or behaviors or things that you described here were anything other than

completely lawful under the standards of the day?

DR. ANDERSON: I don't believe that we were charged to answer questions of lawfulness of the activities. We were charged to answer questions of what the industry may have known regarding the questions posed to us.

DR. SAMET: Greg?

DR. CONNOLLY: Dr. Anderson, you presented a lot of data on intent and a lot of data from marketing groups where there's probably different methodologies, different approaches that make it really hard to analyze. And I think also I'm sort of struck by the federal presentations I see suggest probably a p value of .001. And this presentation, I see stronger words that suggest that the p value is probably higher in terms of drawing each as a causality (unclear). So we're sort of caught here.

I think in looking at marketing documents, there are published literature where there's an attempt to take intent and then link it. I know you were not asked to do that, but

maybe is the committee charged to link it to other data sources, laboratory testing, behavioral population measures, such as do we see higher use by certain brands among groups.

Then I have two questions. Do you think -- what is more important to the menthol smoker, the marketing, the message they provide to the cognitive portion of the brain or the chemosensory effects of menthol on olfaction, tactile perception, and to a lesser extent, gustatory perception? What is more important or are they both linked intimately?

DR. SAMET: And let me rescue you since that question was not necessarily in the charge given to your document review. You can also abstain.

DR. CONNOLLY: Well, but she presented both data sets separately, and I'm asking you can you honestly separate marketing from chemosensory perception. I saw overlap through the whole thing, but it wasn't synthesized, and that makes me feel uncomfortable.

Are there relationships here? Are we looking at one set of PowerPoints where the menthol perception by the individual overwhelms the cognitive marketing, just the fact that it's perceived as cooling tactilely or has an olfactory perception through the olfactory nerves.

Tied to that, did you look at documents on nocireceptors? Did you look at TIMP-8 documents?

DR. ANDERSON: Those presentations are coming this afternoon.

DR. SAMET: Those are coming, Greg. That's the other --

DR. CONNOLLY: Okay. Fine. We can ask then.

DR. ANDERSON: I can speak only to the extent that I can say that my findings of analyses of the internal documents show that marketing plays a role and perception plays a role, physiological perception plays a role. I cannot speak to which is more important.

DR. CONNOLLY: Did you look at

expenditures for marketing versus market share? I'll stop. Okay. But one way to answer that question is how much are they spending on marketing versus market share. Are they spending money on the brand family entirely and then having a low expenditure for menthol and letting the menthol brand itself.

DR. ANDERSON: It's an interesting --

DR. SAMET: It's an interesting question, but let me just say, Greg, these reviews, if you look at the document reviews, they really are segmented without this sort of cross-cutting look that maybe needs to come later.

DR. CONNOLLY: Then maybe it's our job when we synthesize evidence, where we say suggestive, and that evidence, it's stronger, we begin to synthesize so we have a picture of menthol not in segments but in its actual overall impact on the public health.

DR. SAMET: I think if you look at the white papers and the presentations, they've really taken on these separate issues without, as you

say, looking across.

Let's see. I think we had Mark.

DR. CLANTON: I think the presentation very nicely took the data from the tobacco industry and made very clear what their initial intention on marketing mentholated cigarettes was. So I think that's clear and indisputable.

But a question we're going to have to grapple with, and then I'll ask your opinion, is based on newer data in 2006, '7, '8, '9 and '10, was there a change in any of the documents that show a change in intent to market those cigarettes in a way they've been marketed since 1938 or whatever.

I didn't see any, but did you see any in your review of change as we came to more contemporaneous data and expressions of marketing practice? Did you see any change from what had been established in the '40s, '50s, '60s and '70s around menthol cigarettes? Was it consistent? Did it remain consistent? I don't remember what your endpoint was for review, but did you see any

change, because we're certainly going to have to look at that and determine, again, as we see more contemporaneous expressions of marketing, is there a change or is it consistent since the early times?

DR. ANDERSON: Clearly, the marketing of menthol since its inception has been something of a changing process. Initially, it was introduced as an occasional use product for soothing the throat, and we saw that at some point it evolved into slightly more less tangible things such as refreshment and group belonging, youthfulness, that sort of thing.

I cannot speak to how marketing as an entity within the tobacco industry changes from year to year. That's beyond the scope of these presentations. But I can say that I have observed a changing process in the themes of tobacco marketing with respect to menthol.

DR. CLANTON: Thank you. So as one follow-on question, in terms of a more specific kind of change I'm looking for, was there any

evidence of efforts to deemphasize, marketing to younger individuals or African-Americans, mentholated cigarettes as we again move towards more contemporaneous times, the ’07, ’08, ’09, et cetera? Was there any evidence to say we don’t want to market either the way we’ve marketed in the past or to these particular groups of individuals?

DR. ANDERSON: Certainly, I’ve seen that, say, the African-American community, which in most people’s minds is strongly associated with menthol cigarette smoking, is not the only target group of interest. And as with the Salem Spirit campaign that I mentioned in one of the presentations, that was targeted toward a younger audience, and Newport has a very young audience. Different companies and different brands and different line extensions and different times tend to focus on a widely varied but somehow related set of marketing goals.

DR. SAMET: Jack?

DR. HENNINGFIELD: Your conclusions are

very powerful, and I think one of the things that all of us know that have done some document research is that it is a challenge at times ascertaining the degree of your confidence in a conclusion because there are so many documents. You can find a document to support almost anything. I can imagine the tobacco industry charging that you've cherry-picked the documents.

So my two questions that are related are, based on your experience -- and you have a lot of experience in looking at different questions -- what is your own level of confidence that your conclusions are solid? In other words, from absolute to -- and related to that is fitting this into the proposed four-level classification approach that Dr. Samet described at the beginning, the highest level being sufficient evidence and the next one being equipoise or above.

Would you put this in that equipoise and above or into the sufficient to support the conclusions that you've made?

DR. ANDERSON: I see. Okay. Your first question was simply how strong do I feel about the strength of the statements that I made.

DR. HENNINGFIELD: And it may vary across the questions.

DR. SAMET: Actually, let me intervene for a moment because I think the questions you ask are actually the questions that I think we will face, Jack, as we use these reviews. And I think in fairness to Stacey, she was not charged with looking at the evidence.

I think the question of selectivity of these reviews, these massive documents, is something that’s important because I’ve always been impressed that people review as sort of a historical approach and pick the documents that are cohesive in telling a story. And the question of whether that story emerges or this story comes from a prior construct, which might then lead to what you call cherry-picking in selecting those documents to tell a story, I think that’s a complicated balance.

I do think it's for us -- remember my description of these four bodies of evidence that we might turn to, to decide how we will use that one. And I think after we hear the second presentation, I think we should come back to the issue that you raised and in part posed to Stacey. If she wants to address these questions from her own subjective feelings about what she's learned from reviewing the documents, that's for her to do. But I think the questions you're raising sit with us, at least in my mind.

DR. HENNINGFIELD: And maybe, just to make it even simpler, again, just based on your experience -- you do this all the time, so you have levels of confidence when you come to a conclusion. And again, on a scale of let's say 1 to 10 --

DR. ANDERSON: Do I rate a zero or do I rate a 10?

DR. HENNINGFIELD: -- because that's what we'll need.

DR. ANDERSON: Sure.

DR. HENNINGFIELD: I assume it's someplace up here or you wouldn't have come to the conclusions. You do this stuff well.

DR. ANDERSON: I will say first that I disagree with that you can find just about anything to support any conclusion you want to make from the industry documents. It's not the Bible, which is an entirely different thing.

There are things that you absolutely cannot find support for in the internal documents. The repetitiveness with which I found the themes I've presented here today was a bit remarkable, particularly given the amount of time that I had to address the committee's needs. When I see a theme coming up over and over again in various forms from different companies, that seems to be a real phenomenon.

DR. SAMET: Okay. John, I think back to you.

DR. LAUTERBACH: Yes, Dr. Samet, a question to Dr. Anderson here.

How did you tell or differentiate between

statements made by, say, marketing consultants, whatever, versus those made by knowledgeable sensory experts?

DR. ANDERSON: The records of the documents themselves, they're usually dated and have an author responsible for them. They usually are a series of reports that go in revision or a series of correspondences back and forth. So it's often rather clear who is responsible for a statement. In cases that it's not, obviously, I back off on who is responsible for it and attribute it to the company whose collection the document came from.

DR. SAMET: Dan?

DR. HECK: I think there's a lot of worthy conversation on a lot of these topics. I'll try to phrase this as a clarifying question. I was interested in your observation, at least as represented in some of the quotes here, that consumers perceive menthol cigarettes to be less harmful, and then with reference to some early survey information or advertising, the things that

you mentioned.

In light of the 2004 to 2006 NSDUH surveys, more contemporary information showing that, in fact, menthol smokers as a group, grouped by ethnic affiliation or generally, seem to have not that impression at all but seem to regard cigarettes and menthol cigarettes as equally or more harmful, did you notice any trend in an evolution of that public perception from those early days you referred to up through maybe the more modern assessments done by market research?

DR. ANDERSON: I haven't conducted any analysis on a trend, as I think you're asking. What I presented here was an overt understanding toward the beginning of menthol's introduction that these are healthier, these are good for your throat and some discussion from individuals within various companies about the health heritage and the establishment of menthol in the better-for-you arena.

DR. SAMET: Tim?

DR. MCAFEE: I apologize for having to

look away when I talk to you.

DR. ANDERSON: No problem.

DR. MCAFEE: But I had a question. I'm trying to sort through how we would again -- which I think we all are -- how we tie in this voluminous information into making determinations. And I see it as potentially having two quite separate buckets, and one of them gets back to something that Greg had said earlier, which I'm actually not sure how much weighs in, in terms of FDA decision-making, which is essentially intent.

Were the tobacco companies -- did they have information about what was happening, the effect of menthol, and, therefore, they were trying to do certain things for the reasons of trying to get more African-Americans to start, for instance, or that their intent was to put menthol in because they wanted to keep people from successfully quitting?

So there's an intent question, and it seems to me these documents certainly could be quite helpful to us in answering that question;

although, some of this I think, which was actually alluded to, is if we really wanted to go down that path, we'd want to sort out is this just some random comment that a marketing firm that they were consulting with the industry was making or is this, in fact, something which would have much more weight, which is an executive within the company was making the statement.

But then the other question that I had -- and I think there are a couple areas where this might be germane -- is, is there actually useful data that they were conducting studies? A lot of them were market research studies, but there were other ones. And I think in our next set of presentations you're actually going to tell us more about the relationship of menthol to nicotine and the impact on palatability, et cetera, where there might really be some information that we really would like to know more about the validity of the testing.

So I would ask the question, is there anything possibility -- if we honed in on a

couple, could we actually ask the -- essentially, look for source documentation to try to assess it as we would another research or evaluation effort?

DR. ANDERSON: Are you asking for additional research studies?

DR. SAMET: Actually, let me take the question because I think this, again, relates to the more general issue of how we're going to use what is found in the documents. And I think on the question of -- for example, if there were scientific findings reported that we thought were relevant, I think then would come with that is the question of what is the documentation of where those findings came from, whether they were a contract laboratory, an industry laboratory, was there a traceable protocol. And I think we'll have to look very carefully at what might be snippets of evidence or findings, perhaps the full reports, and think that through.

So I think we should keep these -- these relate to these general questions of how the subcommittees and TPSAC will handle the evidence.

And I think after we hear the full set of presentations, I think we'll want to come back to these issues. The issue of intent, I think we have to look at that as it matches with our actual charge.

Greg?

DR. CONNOLLY: Just to respond to Jack, there are published standards for document research, Malone, Balbach, Burrough, Carter. So there are standards. There are published articles in the peer-reviewed literature on the internal documents and on menthol; I think six or seven. This is not peer-reviewed yet. So those documents do exist. They're peer-reviewed.

I think, clearly, intent has been demonstrated, but the value of document research is going beyond reading what this subcontract firm, marketing firm, did, but linking it with the four questions that we raised at the first meeting. I think we laid out at that first meeting four distinct questions which intent becomes part of. And what I would say is you

build on intent by doing external laboratory research on what's suggested here, by looking at the SAMHSA data, by looking at your chemosensory actions on specific nerve sites so that you can show there's interaction on the brain, and you synthesize that information.

So from our federal guests who are giving us p values of .001 and a p value of .1 here, then maybe we could arrive, as Jon said, at our equipoise, I guess that's the term, of where our p value is.

As in FDA, I mean, you're challenged with p values. The public has a very high expectation; if H1N1 is going to outbreak. So if you're a public official, your p value is going to be .1; I want to make sure I'm ready; I'm going to be overly cautious here; whereas if I'm a Harvard scientist developing a vaccine, I want to make sure that vaccine doesn't cut (unclear) my p value as.001.

Our problem is, we've got to take our basic science and bring it in with more of our

applied science and come up with a model and a p value that more reflects both the science and also the public health impact.

I think what we did at the first meeting was excellent, and I think we established four very good questions. The second meeting, we all seemed to go off on our own directions. And I hope at the end of this meeting, we can come to those basic questions we asked, the four questions, and begin to frame what the report would look like.

DR. SAMET: We're going to have two more questions, and then we're done with clarifying questions, unless, John -- we will -- No? You're not next. We have opportunities to come back to more general discussion after the second presentation.

Patricia?

DR. NEX HENDERSON: Thank you for the presentation. I just had a follow-up question. Were there any data that looked at why African-Americans were not switching after starting? So

they started on menthol cigarettes but continued on menthol cigarettes into adulthood. Did you find anything in the documents on why there was very little switching?

DR. ANDERSON: On why there was. Kim Klausner's research on initiation yielded some interesting things about how if one starts with a non-menthol cigarette and switches to menthol, or if one starts with menthol and becomes a regular user, there is very, very little out-switching. The tendency to become quite attached to one's menthol brand and one's menthol level is quite prevalent among menthol smokers.

I think you're asking why that's so.

Is that so, are you asking why that's so?

[Dr. Nez Henderson nods yes.]

DR. ANDERSON: That is not something that we determined in the research that we've conducted for this meeting.

DR. SAMET: John, last question.

DR. LAUTERBACH: Just a concern. I thought we were on clarifying questions as opposed

to statements, and Dr. Connolly was making statements and --

DR. CONNOLLY: I deeply apologize to my dear friend, John.

DR. SAMET: I'm touched by this exchange.

[Laughter.]

DR. SAMET: Now, I think it's lunchtime, and what I'm going to suggest -- so the TPSAC members, we're going to be led to the FDA cafeteria. There's a kiosk out there if you want to use that. For those of you who are not in this privileged group who are going to be led to the cafeteria, I guess you're going to have to go out or to the kiosk.

So what I would propose is that in roughly an hour we try and reconvene, acknowledging that that hour might end at 1:30, but we will start by 1:30. Thanks.

(Whereupon, at 12:16 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:40 p.m.)

DR. SAMET: Good afternoon. We're going to get started, and we're going to continue the presentations of the reviews of the Legacy documents. We have Dr. Yerger here actually in reality and not virtually, and she's going to continue the presentation on the documents. Thank you.

Legacy Documents Presentation

DR. YERGER: Greetings. I'm Dr. Valerie Yerger, an assistant adjunct professor in the Department of Social and Behavioral Sciences at the University of California at San Francisco. I'm also affiliated with the UCSF Center for Tobacco Control Research and Education. I thank you for this opportunity to address the committee. I appreciate your time and consideration.

I've been researching and analyzing publicly-available internal tobacco industry documents since 2001. I helped to establish a team at UCSF to analyze tobacco documents, to

answer research questions posed to us by the FDA regarding what the tobacco industry may know about menthol. Our UCSF research team produced several white papers providing comprehensive reviews of our findings.

My three presentations today will provide a general overview of some of these findings and not a complete record of what is presented in our papers. And for this reason, please refer to our white papers for the comprehensive reviews.

My first presentation will be on menthol sensory qualities and their possible effects on smoking topography. I'd like to acknowledge my coauthor Phyra McCandless, a postdoctoral scholar at UCSF; Kim Klausner; Rachel Taketa of the UCSF Library and Center for Knowledge Management for their support and documents searching, and also Karen Butter, who's our UCSF librarian and vice chancellor for her leadership on this project.

The goal of our research on this particular topic was to determine what the tobacco industry knows about the potential effects that

menthol may have on smoking topography. However, before I get started, I'd like to provide a definition for topography. A number of factors collectively account for smoking topography or how it is a person smokes a cigarette. There are both intra- and inter-individual differences in smoking behavior. Other factors include differences in number of puffs, puff volume, frequency, how deeply one inhales, and how long one holds smoke in the lungs, and how much of the cigarette is smoked.

Following are the questions that we sought to answer. Question number 1 here is provided, what properties does menthol contribute to the smoking experience? Does menthol contribute to the sensory qualities of the smoke and effect smoking topography?

Question number 3, do changes in smoking topography lead to greater exposure to toxic substances, increased nicotine dependence or greater chance of tobacco-related disease?

Number 4, what are the various ways

menthol is measured and how are menthol yields determined? Does the menthol content and/or yield have an effect on how the cigarette is smoked or cigarette preference?

Our last question, what is the relationship between menthol and the intensity in the use of cigarettes? That is, does menthol lead to a higher delivery of smoke per cigarette?

So Dr. Stacey Anderson has already presented slides on our methodology, which was consistently employed throughout all of our white papers. However, for our white paper on menthol's effect on topography in particular, we began our initial searches with the terms listed on this slide, which then led to the development of further search terms and a combination of those terms.

We screened 2,518 documents for their relevancy and duplication of which 252 we believed to be worthy of further review. A subset of 67 documents, which were found to be relevant to the research questions posed for this topic, were

cited in the white paper, and I'll share some of these references in this presentation.

Mentholated products were promoted to offer an alternative to the heavy, harsh, hot and many times unpleasant experience of non-mentholated products. This is because menthol has cooling and anesthetic properties that are dose sensitive and reduce the harshness and irritation of tobacco.

This 1978 memo that was written by the Roper Organization to the Philip Morris marketing and consumer research departments addressed menthol properties. And it reads, "The Richmond meeting confirms certain theses that we had that there are physiological effects from menthol and that menthol has a slightly local anesthetic effect, and these effects are preferred over taste."

Menthol's cooling effect is a result of a chemical action that occurs at or near nerve endings associated with the sensation of cold that are located in the nasal, oral and skin membranes.

Menthol has the ability to undeniably impart a cooling influence, and in doing so, reduces both harshness and tobacco taste. Menthol's impact is short-lived and incorporates the initial wave of the cooling effect and occurs in the upper back throat immediately upon inhalation.

A number of menthol's properties are described in a 1972 Brown & Williamson report. "The delayed, more persistent and pain-suggestive sensation is designated an irritation. Menthol irritation becomes apparent immediately at the short-lived menthol impact has subsided. Menthol irritation is predominantly cooling and tingling."

Menthol has analgesic properties. Analgesia is the absence of sensibility to pain. An analgesic is an agent or drug that alleviates pain without causing loss of conscious. Menthol's analgesic properties were described by a Brown & Williamson researcher who provided the following quotes: "Menthol in cigarette smoke is a local analgesic and that it apparently and/or absolutely reduces the intensity of tobacco pain, suggestive

sensation in the mouth, throat and nose." And the second quote is, "It is not known whether smoke menthol acts as a drug-like analgesic reversibly impeding nerve impulse transmission or as a mental analgesic which is causing reversible loss of ability to recognize or identify pain sensations, or as both."

Taste is important to the industry as the viability of their products in the market is dependent on taste. According to a 1981 Philip Morris document, "Tobacco manufacturers interchange physiological effects with taste."

This 1984 R.J. Reynolds' document discloses that, "Menthol taste and coolness measure the same dimension. However, coolness as a descriptor is used only with positive perceptions of menthol taste, intensity, delivery sensations. Coolness is a function of menthol. Coolness is a sensation more than a taste. It can be negative in terms of too much menthol. Refreshing is an element of coolness."

In its 1992 focus group study, Philip

Morris intended to collect data to be used for developing a new menthol product. Participants reportedly seemed to like menthol because it buffers, masks the taste of tobacco. Philip Morris decided that further exploration of position ways to leverage this masking effect may be warranted. “It is during the exhalation phase, according to the panelists, that menthol masks the taste of tobacco, making the smoke smoother.” However, the menthol smokers in the study also noted that inhaling cigarettes with too much menthol elicited a bite that actually hurts.

Does menthol contribute to the sensory qualities of the smoke and affect smoking topography? The answer is yes, but it depends on the level of menthol and nicotine in the cigarette.

In 1983, a confidential R.J. Reynolds memo written by the company’s chemist may provide insight as to how the interaction between nicotine and menthol is taken into account when engineering tobacco products. “Nicotine is a major irritant

in cigarette smoke. While menthol is known to alleviate sensations of irritation, balance between the irritation of nicotine and soothing of menthol is important." And, for instance, in the case of two cigarettes at the same nicotine but different menthol levels, the product with more menthol might appear to be less irritating.

In terms of contributions to sensory qualities in smoking topography, as menthol level increases to a certain point, the time between puffs also increases. Increased time between puffs is associated with satisfaction from the previous puff, and the fewer the puffs, the more satisfying and accepted a cigarette is.

In our allotted time, we were unable to locate documents providing evidence that the industry addressed this question regarding topography leading to greater exposure of toxic substances, nicotine dependence or tobacco-related disease. However, documents showing a link between menthol and increased nicotine dependence and menthol's role in the health effects of

smoking are discussed in other papers presented today.

Menthol is measured in milligrams or micrograms that are distilled from a cigarette before and after smoking. Because of its highly volatile nature, tobacco companies sought patents on technology developed to reduce menthol migration from one part of the cigarette to another.

Menthol is applied to cigarettes by a number of methods shown up here on this slide. It’s either sprayed onto cut tobacco or a tobacco stream, applied to paper, printed on pack foil, or dissolved in filter plasticizer.

According to an undated report on product development, the level of menthol in U.S. domestic products by weight was reported to be .34 to 1.25 percent with the lower levels for emerging menthol markets. The document does not define emerging.

Smoke studies on mentholated cigarettes have shown similar results for the amount of unchanged menthol in mainstream smoke, sidestream

smoke, and in the filters and butts. The total amount of menthol available to mainstream smoke ranges from 30 to 35 percent of the applied level. Tobacco manufacturers measured the menthol content by isolating menthol by steam distillation followed by gas-liquid chromatography.

To determine menthol yields, the tobacco companies used smoking machines. Mathematical models were developed to estimate smoker intakes of nicotine, tar and total particulate matter because smoking machines do not accurately reflect actual human smoking conditions. And as previously mentioned, menthol yields are measured in milligrams per puff or micrograms per puff.

Tobacco manufacturers knew it was not enough to know total menthol content and yields, and they sought to understand menthol delivery. Smoker acceptability is based on the perception of menthol; that is, whether a smoker recognizes menthol in the cigarette.

Factors affecting menthol delivery include its puff profile, depending on whether

menthol is applied to the filler or to the filter during the preparation of the cigarettes. The more menthol that is applied to the filter and the shorter the age of the cigarette, the higher the delivery of menthol in the first puffs. And menthol migration affects puff-by-puff menthol delivery. So storage time and storage temperature are important.

Menthol content and yield have an effect on cigarette preference, but it’s unclear from the tobacco industry documents revealed in our searching whether these affect how the cigarette is actually smoked.

Philip Morris found that smokers who perceive their cigarette as being more acceptable may also perceive cigarettes as having a medium level of menthol. When testing new prototypes of its Salem brand, R.J. Reynolds found that the low tar menthol smokers wanted cigarettes with less nicotine delivery and more menthol delivery, whereas full-flavor menthol smokers wanted high levels of nicotine deliveries and low or moderate

deliveries of menthol.

R.J. Reynolds tested the preferences of women, grouping them into groups, 18 to 34 and 35 and older. The study concluded it takes less absolute menthol delivery to achieve the younger group's higher ideal than it takes to achieve the older group's lower ideal.

In searching the documents, terms related to intensity of cigarette use and menthol did not return results related to the sixth question posed by the FDA; therefore, it's unclear what the tobacco industry knows about the relationship between menthol and intensity in the use of cigarettes.

So to summarize, using the tobacco industry's own words from their documents, "The sensory qualities of menthol affect smoking behavior and cigarette preference. Menthol has physiological properties that mask and buffer the harshness and irritation of tobacco due to its cooling effect, local anesthetic effect, and its analgesic effect."

Perhaps this quote that comes from a document about Project Crawford, which was located in the British American Tobacco Company collection, helps to further summarize this presentation. “The whole smoking experience thus becomes much more pleasant. Negatives are minimized; that is, tobacco taste and harshness. Positive attributes are superimposed, coolness and menthol taste.”

So that’s it for this presentation here, and I’ll move on to the next one. And these are actually the references used for this presentation, and all these references are located in our white papers.

The goal of this research was to determine what the tobacco industry knows about the potential effects that menthol may have on nicotine dependence, and we sought to answer the following questions:

What are the addiction and exposure measures and what are their relationships to menthol cigarette use?

Do menthol smokers show greater signs or higher levels of nicotine dependence compared to non-menthol smokers?

Third question, does menthol affect cigarette consumption; that is, cigarettes per day?

Do menthol smokers smoke more or fewer cigarettes per day compared to non-menthol smokers?

What is menthol’s effect on nicotine metabolism?

Do menthol smokers experience altered nicotine exposure and/or altered nicotine metabolism as compared to non-menthol smokers?

Does menthol have an effect on nicotine delivery?

Does menthol alter the addictiveness of smoking through sensory stimulation?

Here are the key points regarding the methods that specifically pertain to this paper. The Legacy Tobacco Documents Library was searched using keywords and phrases such as “menthol

combined with nicotine dependence," addiction and brand names such as "KOOL," "Newport" and "Salem." This initial set of keywords resulted in the development of further search terms in combination of keywords such as "menthol pharmaco," "menthol/nicotine interaction" and "nicotine delivery." Reports, scientific research and correspondence were reviewed for relevancy.

For our white paper on menthol's potential effects on nicotine dependence, we screened over 10,000 documents for their relevancy and duplication of which we found 309 to be worthy of further review. A subset of 72 documents, which were found to be relevant to the research questions posed for this topic, were cited in the white paper. And, again, I'll share some of these references in this presentation.

The addiction and exposure measures identified in the documents were the Fagerstrom Test of Nicotine Dependence, FTND, which is used to measure nicotine dependence. Cotinine, carbon monoxide, carboxyhemoglobin and thiocyanate were

identified as the biochemical markers used to measure cigarette smoke exposure.

In our allotted time, we did not find documents linking the FTND with menthol. Overall, we found few documents showing the tobacco industry conducted research on the exposure measures in menthol or comparative data on menthol smokers versus non-menthol smokers in terms of these exposure measures. And for this particular question here, we located no documents presenting any evidence of industry research specifically linking menthol to addiction or to the biomarkers of tobacco exposure measures.

According to industry-funded research and research conducted internally by tobacco companies, menthol has no effect on nicotine absorption, nicotine metabolism or nicotine dependence. However, we located documents showing industry studies on nicotine and cotinine, which excluded menthol smokers.

According to Brown & Williamson, although they had considered in 1985 to do comparative

blood cotinine testing on menthol and non-menthol smokers, subsequent searching the Legacy Tobacco Documents Library did not reveal evidence that this research was actually done, as was the case with R.J. Reynolds. And this just shows the Brown & Williamson document where participants had to be smokers of non-menthol cigarettes.

So despite smoking fewer cigarettes per day, black smokers reportedly have higher serum cotinine levels than do white smokers. This suggests the metabolism of nicotine or the excretion of cotinine may differ by race. As the majority of black smokers smoke menthol cigarettes, investigators have suggested menthol may play a role in the differences in nicotine metabolism observed between black and white smokers.

A 1995 document revealing comments prepared by Philip Morris to address claims about menthol that were made in a class action suit filed in a U.S. district court contains marginalia regarding these noted racial differences.

According to these handwritten notes, “Menthol is not the culprit. Rather, it’s the African-American living conditions such as lower socioeconomic status and less desired location of where they live, exposure to dirtier air, city and pollution.”

While much research has been done to demonstrate that race is a social construct and not a biological one, the tobacco industry says that those studies investigating whether the presence of menthol in cigarettes increases either the cotinine or nicotine levels have for the most part failed to take into account both the ethnicity of the study subjects and the nicotine yields of the cigarette smoke, thus stating that ethnicity is a confounding variable that influences serum cotinine levels, especially given the absence of an assumed and claimed effect of menthol.

We located no evidence that tobacco manufacturers conducted epidemiological studies that could answer this question from an industry

perspective. However, tobacco documents reveal that despite the industry's claim, that menthol is only a flavorant. The addition of menthol to cigarettes masks the harshness of tobacco and provides an extra something which makes cigarettes more desirable to some smokers.

According to the tobacco industry, menthol is only a flavor additive, as it says here. However, we located documents that show the tobacco industry was aware that menthol had properties other than flavor. In 1982, a document located in the British American Tobacco Company collection discloses conclusions made from a qualitative study done in consumer perceptions of menthol cigarettes. "Menthol cigarettes undeniably impart a cooling influence. It is the cooling effect which constitutes the major attraction, this and the concomitant reduction in both harshness and tobacco taste. Menthol smokers build up a tolerance to this menthol taste, but menthol's effects are still present."

The 1979 Roper report on a qualitative

study conducted by Philip Morris concluded that, “Menthol has properties of a drug,” and the properties are listed up above here.

Menthol has non-flavor-related effects on the unflavorable aspects that accompany cigarette smoking. The Project Crawford report previously mentioned provides additional insight into menthol’s masking effects. “There is no question that menthol has a significant masking effect on both the taste of the tobacco and the harshness of the smoking experience.”

A 1976 confidential R.J. Reynolds’ interoffice memo written by chemist Dr. Mary Evelyn Stowe (ph) to Dr. Donald Peele (ph), manager of the company’s chemical research division, discloses that the tobacco manufacturer had known that, “Even at low or subliminal levels, menthol reduces nasal sting, tongue bite and harshness.”

When discussing competitors, Philip Morris and Brown & Williamson, about their product philosophies, R.J. Reynolds note that, “Their

competitors appear to design products primarily to deliver optimum nicotine impact and satisfaction. Philip Morris appears to be far more sophisticated in this respect than Brown & Williamson who, of course, can mask a multitude of sins behind menthol."

Tobacco documents suggest nicotine and pH levels and not menthol determine cigarette consumption. Philip Morris in particular found cigarette consumption to be related to the level of tar in cigarettes. However, among non-menthol smokers was the fear that switching to menthol cigarettes would increase their consumption. However, smokers of non-menthol cigarettes reported that one of the deterrents to their switching to menthol cigarettes, even among those who do like the taste of the menthol, is the fear that their smoking volume would automatically increase.

These are quotes from a couple of the participants in this study, one of whom said, "I seem to smoke more and therefore, you are getting

more nicotine and tar into your body." And a second participant, "Well, I find them easier, so it's easier to pick one up and light one, whereas if there was an ordinary cigarette, I would probably turn it down."

It is unclear what the tobacco industry knew about the relationship between menthol and nicotine metabolism or if menthol smokers experience altered exposure and/or altered nicotine metabolism than non-menthol smokers. However, tobacco company researchers reviewed the scientific literature and concluded that menthol did not induce hepatic cytochrome P450, at least in rats.

But not all of the menthol appears to be conjugated. A study commonly cited in tobacco documents showed, in the oral administration of menthol induced in rats, cytochrome P450 and its corresponding enzyme, as shown here by a couple of the documents that we located.

The answer to this next question is yes, tobacco industry documents revealed menthol has an

effect on the amount of nicotine delivered in smoke. Tobacco manufacturers came to discover they could manipulate the level of tar and nicotine in their cigarettes and with the help of menthol design acceptable cigarettes that could meet consumer demand for reduced tar and nicotine.

Impact is perceived by the smoker as a kick or grab in the back of the mouth and throat when inhaling a cigarette. It’s been demonstrated that this physical tracheal stimulation is crucial in providing much of the immediate satisfaction gained from smoking. Tobacco manufacturers can predict the amount of menthol needed to attain a desired impact at any given nicotine level. Specific combinations of menthol and nicotine affect perceived impact.

The trigeminal nerve is the fifth cranial nerve and is widely distributed throughout the head. Trigeminal chemoreception was of interest to the tobacco industry as nicotine also stimulated this nerve. The trigeminal is essential to eliciting a liking response for a

tobacco product.

Philip Morris conducted research to find other compounds that could evoke comparable physiological effects as nicotine. So Philip Morris established this trigeminal panel in August of 1989 in order to screen for compounds which might possess these nicotine-like sensory characteristics. And it shows here what the purpose of the trigeminal panel was, to identify compounds.

The thing to note in this figure is how impact, which is along the Y axis, goes up as the nicotine level goes down while the menthol also goes up.

Menthol exhibits nicotine-like properties that stimulate sensory receptors, which could contribute to addiction by strengthening the conditioned aspects of smoking. So menthol produces nicotine-like effects on the central nervous system. It stimulates the trigeminal co fibers, the gustatory, or the taste, and olfactory, the smell, nerves and nociceptors.

Menthol's cooling effect alleviates nicotine's irritating effect.

Our analyses of these documents indicate, one, that menthol is used in cigarettes to override the harsh taste of tobacco. Menthol has physiological effects, and it synergistically interacts with nicotine. Menthol makes low tar, low nicotine tobacco products that would otherwise be tasteless and unsatisfactory, acceptable to smokers. Tobacco manufacturers manipulated menthol levels to produce tobacco products that would be easier to consume, especially for new and inexperienced smokers.

Here's a quote from a British American Tobacco document that says, "Since menthols undeniably impart a cooling influence and since a byproduct of this is to reduce harshness and to modify or mask the tobacco taste, if it manages to alleviate symptoms such as when the user has a cold, is it, in fact, a less harmful method of ingesting tar and nicotine, or does it simply seem to be less harmful because it is more palatable?"

And here are references that we used for this particular presentation.

Now, the goal of this research was to determine what the tobacco industry knows about menthol's potential health effects. For a comprehensive review of the findings, please refer to the appropriate white paper which was written by my colleague at UCSF, Dr. Maria Victoria Salgado.

Today, I will present a general overview of some of these findings. And the questions that we sought to answer on this paper: What is the overall pharmacology of menthol?

What are the major pathways of metabolism of menthol?

Does menthol affect the rate of carcinogen metabolism?

Question number 3 is a set of questions related. They are what is menthol's impact on biological mechanisms?

Does it alter the body's burden of cotinine and carbon monoxide?

Does menthol alter detoxification of carcinogens delivered in cigarette smoke?

Does it alter permeability of cell membranes?

The last question, what is menthol's possible role in disease risk; that is, cardiovascular disease, cancer, respiratory illness, mental health among others?

We began our initial searches with words and phrases such as "menthol combined with side effects, adverse effects, carcinogen, pharmacokinetics, pharmacodynamics." Reports, scientific research and correspondence were reviewed for relevancy. We screened over 4,000 documents and found 189 of them worthy of further review. In the white paper, we cited a subset of 31 documents that were relevant to the subject areas of the research questions, and I'll share some of these references in this presentation.

Menthol can be absorbed orally, cutaneously through peritoneal injection, and through inhalation. Menthol is metabolized in the

liver via conjugation with glucuronic acid, then the conjugated menthol is excreted in the urine.

Some documents analyze the potential for carcinogenesis of menthol itself as these two sample documents indicate. The first document is a 1963 Liggett & Myers document that discloses the incidence of tumors was not significantly different from that observed with condensates from non-mentholated cigarettes. The second document is a 1993 Philip Morris finding on one of its in-house studies on menthol, showing no evidence of carcinogenic activity in rats or mice.

In the allotted time that we had, we didn’t locate documents that analyzed the potential carcinogenic effect of menthol that reported any positive findings.

In 1997, Lorillard published the following study where two different groups of rats were exposed to inhaled smoke from either non-menthol or menthol cigarettes for an hour a day, five days a week, over the course of 13 weeks. The objective was to determine any significant

alteration of smoke-related biological effects resulting from menthol addition.

In the sample were 42 rats exposed to non-menthol smoke and 30 rats exposed to menthol smoke, the final conclusion stated that, “Results do indicate that the addition of menthol to the tobacco did not significantly alter the serum nicotine or cotinine levels, and that the addition of menthol to cigarettes does not significantly alter the pattern, incidence, severity or reversibility of any of the effects attributable to smoke exposures in rats.”

In our allotted time, we were not able to find documents that linked menthol to detoxification of carcinogens using research conducted by the tobacco industry.

Regarding the effect of menthol on cell permeability, a study published in 1983 analyzed the toxicity of menthol on four different in vitro systems covering organ cellular and subcellular levels. In that article, authors suggested that one effect in menthol is a deterioration of

biological membranes, and this study was partially funded by the Swedish Tobacco Company.

We were not able to find documents related to menthol and disease risk except for cancer, an issue that was previously addressed. However, we do know that the industry conducted literature reviews, as shown by these two documents, R.J. Reynolds reported in a 1984 document that, “No long-term studies greater than a year of the effects of menthol cigarettes were found in the literature.” And a 1999 Philip Morris document that reviewed the literature remarked that, “Most studies using human subjects were case reports, and conclusions were, therefore, anecdotal.”

A 1984 document from the R.J. Reynolds collection summarized toxicological data on the short-term clinical effects of menthol as the following, “In dermal testing in humans, menthol was nonirritating. However, in certain rare instances, menthol has been reported to cause adverse reactions in some individuals. Most of

these effects are manifestations of allergic hypersensitivity. They are transitory and rapidly disappear when exposure to menthol is ended."

So, in summary, most of the information tobacco companies used and based their decisions on came from the biomedical literature and not from studies carried out by the companies themselves. And data about menthol's effect on biomarkers of smoking exposure found among the documents tend to suggest that menthol does not affect the levels of those biomarkers.
And the study cited by the tobacco industry may be underpowered due to small sample sizes.

It is not evident, from searching the tobacco library documents, that menthol has adverse long-term effects, although the industry recognized that well-done research had not been conducted in this area. This lack of information makes it difficult to analyze menthol's role in disease risk.

In addition, short-term effects seem to be rare. And regarding its role in

carcinogenesis, it seems that the industry view is that menthol has no carcinogenic effect itself and it does not increase the carcinogenic risk of other substances, although we were not able to find documents to support this. And here are the references for this presentation.

I actually had another presentation that's not loaded up, our closing remarks. I can just read them. And I also wanted to present to you the rest of the members of our team because there were quite a few of us. In addition to Stacey and myself, we had Kim Klausner and Rachel Taketa, who were helping with our document searching. Maria Victoria Salgado was another researcher that was helping, and Phyra McCandless was a postdoc helping. And I just wanted to acknowledge their assistance.

But I also want to leave you with some closing remarks. Regarding the direct health effects, there appears to be a marked absence of industry research on menthol's direct health effects. And menthol is a local anesthetic, which

makes menthol cigarettes easier to smoke than cigarettes with no menthol added. Menthol facilitates smoking due to the anesthetic and cooling effects and confectionary and minty medicinal flavors, which contributes to smoking initiation among inexperienced and young smokers.

Menthol inhibits smoking cessation. When a smoker has a cold or sore throat, menthol makes it easier to keep smoking in spite of discomfort;, perceived health benefits or relief that will reduce negative health effects of smoking; and due to the odor of its smoke, menthol cigarettes are perceived by some to be more socially acceptable than are non-mentholated cigarettes.

So independent of whether menthol as an additive is a carcinogen or has direct effects on disease causation, menthol’s role in initiation of smoking and inhibiting cessation contributes to the overall burden of tobacco-related disease. Menthol’s presence in tobacco products indirectly promotes tobacco-related disease and has a negative population health effect.

Okay. That's it.

Clarifying Questions

DR. SAMET: Okay. Thank you for your presentation. Thanks to you and your colleagues for what must have been a lot of work over the last few months.

I think again, in the spirit of the comments following Stacey Anderson's presentation, I think clarifying questions would be useful. I think the same general issues that we had in our last discussion remain pertinent, and I think we need to have some discussion about them.

So let's see, questions here. John?

DR. LAUTERBACH: Dr. Yerger, what steps did you take to verify that the information you presented here is accurate and that the people you're quoting in these documents have the technical skill and knowledge to come to valid conclusions?

DR. YERGER: Well, we were given the task of identifying information in the tobacco documents, and that's what we did. Those of us

who have been looking at tobacco documents have seen a number of the names, and there are other sources to verify years that they were employed at a particular company and what their title was at that time.

So what we presented to you is what comes directly out of the documents and not our interpretation of what's there. And that's why we take great caution to provide the citations so that people can easily identify these documents and go back.

DR. SAMET: John, is this a clarifying question?

DR. LAUTERBACH: The report on Project Crawford, are you aware what country that was done in?

DR. YERGER: No, but I know that it was reported in a U.S.-based tobacco company.

DR. SAMET: Okay. The question's been asked and answered.

Other questions? Dorothy?

DR. HATSUKAMI: This is somewhat to the

question that Jack had asked Dr. Anderson. But if you could give me an idea in terms of what are some of the criteria that you used to come to a conclusion. It seems like Dr. Anderson had mentioned the repetition of finding in the industry documents, potentially looking at the convergence of the finding across different sources. And do you also take into account the source of the document as well? I guess I wanted to get a clearer picture in terms of what makes you decide that this, in fact, is a solid conclusion.

DR. YERGER: Well, I think our conclusions were basically what was presented in the documents. The closing remarks that I gave at the end were themes that were recurring across the various topics that we were looking at. So there was some sense that -- whereas Dr. Anderson was working on her particular topics, I had my topics that I was working on. We were finding that we were coming up with some of the same conclusions across the topics, and that seemed kind of

important to report on. But we did try very hard not to put our own opinion in this. That's why it's very powerful to use the industry documents because we can use direct quotes.

DR. SAMET: Greg?

DR. CONNOLLY: Thank you very much for your work on this.

Again, I would just remind the committee that there are other papers researching the internal documents that have been published in peer-reviewed journals that contain quite a bit of good information.

I think you demonstrated intent quite well, but I come back. Did you look at TIMP-8 receptors, nocireceptor research, olfactory research?

DR. YERGER: I think that's an excellent suggestion, and had we had more time, we would have done that. I think it's also important to know that this is also a suggestion of where additional research and searches can go. We were kind of limited, Greg, in our amount of time that

we had.

DR. CONNOLLY: It would just be an observation that you made a number of observations about the product, but to have it more grounded in the chemosensory effects. And some of the terminology was sort of difficult to follow, then that would strengthen some of the statements. But I think to ground it more in terms of industry research into the chemosensory effects, particularly the TIMP-8 or TIMP-3 receptors, the nocireceptors, the olfactory cascading effects, then it produces a much richer body of evidence for the committee to deal with.

DR. YERGER: Yes, no doubt that’s the case. We did make reference to other published studies on tobacco industry documents that will provide some additional input there.

DR. SAMET: John?

DR. HECK: I guess it’s more of a discussion matter rather than clarifying so maybe I’ll deal with it later.

DR. SAMET: Jack?

DR. HENNINGFIELD: One of the things that we're hoping to learn from the industry and haven't yet, and I'm wondering if you saw anything, was on the effects of menthol where they're talking about low levels of menthol, where the cigarettes might not be branded menthol. And I'm not sure if from what you saw that it was possible to make that separation.

DR. YERGER: Yes, unfortunately, that was not one of the research questions. We were strictly posed with looking at identified mentholated products.

DR. HENNINGFIELD: And let's see, at this point, we're still just focusing on this or both UC --

DR. SAMET: I think at some point I would like to close out clarifying questions on this and move to the general discussion. So I think, again, clarifying questions related to Dr. Yerger's presentation is where we should be now.

So Tim?

DR. MCAFEE: Yes, I had a very specific

question relating to the graph that you showed us about the nicotine effects on impact of varying menthol deliveries, and I've read the text in the white paper. And, basically, my question -- since this is a rather dramatic finding, which I think will be very important to our work, it's whether -- if we were to go back, which I will probably try to do tonight, but go back and look at the actual document that you're doing, are we just going to see the graph or is there like 15 pages of material describing whether they did this with eight people or 80 people? Will we be able to learn enough to get more of a grasp of how reliable the finding is, really, from a scientific perspective as opposed to an intent question?

DR. YERGER: I think if you go to the actual tobacco document, which is cited in the white paper, that you might get some of your questions answered. Unfortunately, from what I've seen, they weren't very clear about their actual study design and sample sizes.

DR. MCAFEE: And again, just if I'm

reading this right, what it's basically saying is that if you get the level of menthol high enough, even with no nicotine, people found the cigarette --

DR. YERGER: The impact scores were high.

DR. MCAFEE: -- the impact is actually higher than the high nicotine cigarette.

DR. YERGER: That's what that graph indicates, yes.

DR. SAMET: Okay. Now, we're still with clarifying questions from others. Mark?

DR. CLANTON: I have a question, if you came across any incidental findings. And what I would ask you about is, was there any finding that described how they used the information to alter the manufacture of cigarettes or alter manufacturing practices? And the reason I ask that is because, at some level, it's almost irrelevant as to whether the science they looked at was good or bad, it's what they believed. It's what they had.

So I'm curious, any incidental findings

that said based on what the industry had at hand, that they made decisions about either manufacture or marketing?

DR. YERGER: Yes, I don't really think that's a clarifying question, and I'm thinking that that might be something that you might find in one of the white papers on consumer perceptions.

DR. SAMET: I'm going to make the suggestion that we move to what I think is, to me, the most critical issue, which is how do we use the information from the document reviews. And I think, also, whether, having seen these broad reviews that have been done, there's any way that if there is the opportunity to ask for a bit more work or some focusing, that would be of benefit to us as we look at the report. And I think, to me, the most obvious question and possibility is whether there could be a relook -- obviously, it would have to be a quick relook -- at these topics, focusing the reviews on the last five or ten years, or some interval that is most germane

to our report. I think that, yes, some of the findings will be generally relevant, but I think some of the findings are much more time-context specific.

So I think first I would ask -- I don't know whether what I'm proposing is possible or not, and I think that's a question perhaps, Corinne, to you. And then I think also whether the committee feels that if we are going to use the -- as we look at the information from the documents, we could make it most relevant to our task at hand perhaps with this additional focusing.

So first, Corinne, and then just on the potential, and then we will go after --

DR. YERGER: Excuse me. I have a clarifying question. Do I stand here still or you guys need me to stay here?

DR. SAMET: I would urge you to duck for cover.

[Laughter.]

DR. CONNOLLY: That's not a clarifying

question. And, yes, you can step down.

DR. SAMET: Sorry. Thank you very much. We may have questions for either you or your colleague, Dr. Anderson.

DR. YERGER: Okay. That's fine.

DR. SAMET: Don't wander too far.

Corinne?

DR. HUSTEN: And I would need to check, obviously, in terms of mechanisms but also the availability of researchers to do the analyses. So we can check on that and let you know.

DR. SAMET: Okay. So let me open up the floor then for general discussion of the documents and our use of them.

Greg?

DR. CONNOLLY: Well, I'll first comment on just history and what we should be looking at. I'm a firm believer that science is cumulative, that science is accumulation of knowledge over time that's refined, so that, in a sense, it's saying we're not going to consider the British position study, because it was done in 1951, in

our assessment of lung cancer risk. So I would be more open than trying to set limits. I think it's unfair to the committee to set limits. There is science that is there.

DR. SAMET: Just a clarifying comment, I was not proposing setting limits but proposing that a more intensive delving into the most recent --

DR. CONNOLLY: Well, let me --

DR. SAMET: -- might be most valuable.

DR. CONNOLLY: -- finish my point in that since the industry's been required by the MSA to report, there could be a bias effect on what documents are produced internally within the industry. So for the most recent information, I would believe that we're more dependent upon industry full disclosure, as a drug company would do for another agency, than relying upon documents because of a bias effect. And then even because of that bias effect, knowing that in civil litigation, anything is discoverable, there may be a less likelihood of people in industry putting

things in writing or making comments. So that is, I think, a fact that we must consider in looking at documents.

I believe science is cumulative. If there is evidence that goes back 20 years, it's valid. If it's good, it should not be excluded. So that is my comment.

I think the other point is a picture is beginning to emerge, and I think it goes back to the four questions we asked. But this presentation, again, is looking at one piece of that picture, maybe misinterpreting some of the terminology. But a picture is beginning to emerge that we can work this information into the picture but not necessarily rely on it as a solution. But I think it is important.

The final thing I would say is that one of the manufacturers submitted a series of statements about menthol, and I would kind of like to ask Valerie just to give her opinion on these statements. But I think the statements made on menthol by industry are worth taking a hard look

at and looking at both internal documents and other research.

Finally, I would enjoy hearing from menthol experts, scientists like Cabal (ph), Eckels, others before the committee where we can get into a very active dialogue upon the science. And that's not to diminish in any way, shape or form what we've heard, but I think to really delve into this issue, talking to people that have spent their life studying menthol and understanding the chemosensory effects, how does impact affect dopamine release, how does it affect the limbic system, how does it affect actions of the basal ganglion and topography? If we want to get the science, that's where I think we should be directing ourselves towards.

DR. SAMET: So just a comment and reminder that the subcommittees, again, as they feel they need additional experts or people to be brought to writing group subcommittee meetings, that is the opportunity for such individuals.

Let me just canvas. I'm not sure we have

a complete list of who else wants to comment at this point. Okay. John?

DR. LAUTERBACH: Yes, Dr. Samet. I have a grave concern about the scientific credibility of the presentations we just heard, and we're told that menthol in tobacco is measured by steam distillation followed by gas chromatography. I think even Dr. Ashley would not do that in his laboratory. It's been GC for umpteen decades now. This information is easily obtainable and would have come out of any reputable search of the literature in the UCSF collection.

The study there of Brown & Williamson mentioned with the Fagerstrom, that was a one off study that was published in an article by Gori and Lynch. It had nothing to do with menthol at all. It was a study in defense of the Barclay cigarette.

Several of the other things mentioned here, Project Crawford had nothing to do with the United States, nothing to do with U.S. style menthol cigarettes in the least. And, again, some

of the comments here, both here and in the Reynolds' document, I'm familiar with some of that literature, were basically technically inaccurate statements that would not survive good peer review.

DR. SAMET: So I think the issue is that the UCSF group was asked to review the tobacco documents and provide an accounting of what was in those documents. And if they were correct in carrying out their task, what we should have heard is an accounting of what was in those documents, whether there were inaccuracies contained within those documents or not.

I think the general point is how we as a committee use the findings of these searches to the extent that they provide information that is useful. I think we have to carefully evaluate that, and whether there are important findings that we may regard as important for which documentation is inadequate, I think we'll have to think that through very carefully.

Let's see. Patricia?

DR. NEZ HENDERSON: I'm still having a problem with the I guess the information that's been given to us or the lack of information that's been given to us. We had requested several meetings ago that the industry provide information on marketing in terms of how much dollars is spent, particularly on African-American communities, and that information has still yet to be given to us. I think it really speaks to the high volume of African-Americans smoking menthol cigarettes. So I guess I would just request that from the industry.

DR. SAMET: I think we'll have an opportunity perhaps -- Corinne is going to be speaking in a little bit. You can readdress that question at that point.

Dan?

DR. HECK: I have little doubt that the UCSF team did execute their requested mission here as they did. I think, though, that what we've seen today presented kind of speaks to the frailty of that approach. We've seen both in the

literature in recent years and in, indeed, the industry presentations offered at the invitation of the committee in July, quite a few of these areas have been researched rather intensely in recent years or decades even. And, no, those findings aren't old enough to be housed at the UCSF archive at this point. A good number of those have found their way into the published peer-reviewed literature.

So I think that the snapshot we get from the '70s, '80s, well, a few into the '90s perhaps here, particularly these marketing surveys, a consumer products company using these marketing firms to look at users of competitive products to determine what is appealing about them, how can they get that business, this is fairly mundane consumer products company behavior.

I think some of the things that Greg mentioned, looking for translation of some of these anecdotal or survey findings or speculation from the '70s into modern contemporary language regarding topography, neuropharmacologic or

neurological or sensory effects and the effects on the biomarkers, these studies have been done in recent years. The methods didn't exist in the '70s.

So I think we're maybe asking these documents to do a little too much, looking for a contemporary interpretation of science that really didn't exist in a very sophisticated state in those days.

DR. SAMET: Cathy?

DR. BACKINGER: I'd just like to make a comment on that because I don't even remember what year off the top of my head, but I think this goes back to something that Greg brought up. This tobacco industry documents research is considered a legitimate area of research. When Bill Clinton was president, he signed an executive order that basically ordered NCI and NIH to make the documents available for research. And from that time, we have built a whole discipline and methodology around the use of these documents. And so, while they may not be, as you said, the

current science, they certainly provide insight into what the tobacco industry was thinking at the time and what they believed and their intent.

And, yes, you-all will have to figure out how that's going to play in with the report, but I don't want to discount, I don't think -- from the NCI perspective at least, discount the value of tobacco industry document research. There's a lot of people that publish in this arena. It's in peer-reviewed published literature, and so there is a value to it. And to just discount it based on the fact that it's old, I don't think is a legitimate reason.

DR. SAMET: Okay. I want to go back to sort of the question I put on the table, which is, is there anything that we could ask for that would make these documents and the reviews that have been done today more useful for our purposes? Let's just focus there because I think we need an answer that could be yes or it could be no. And then I think if it's yes, then we ought to say what else might be done and then turn to FDA and

ask if it can be done.

Mark?

DR. CLANTON: I think I asked a question before our break, that might be responsive to your question, and it has to do with chronology. So, for example, if African-Americans and youth and beginning smokers somehow got targeted based on this old data, the issue is, is was there a change at some point whereby they went against that tide or has there been a continuation of marketing practices based on these old beliefs and old data?

The reason I ask that question, and would love to see exactly what the chronology is in marketing and use of the data, is because if there's been no change at all, the new science may be irrelevant. If the same groups are being targeted for the same reasons they used to be targeted, then new data, new science, better science may not be relevant in terms of how we look at how that data was used.

So I think knowing whether it's 2004 forward but looking at the same kind of data,

asking the same kind of questions that came from these older, historical surveys of the industry, getting that data and see if it's the same, then, in fact, we don't have to worry about the integrity of the data that much.

DR. SAMET: So, actually, Mark, we will have a writing subgroup working on this topic, and I think you're describing the telling of a story that, in fact, the UCSF reviewers were not asked to tell. But it's one that perhaps the authors of this chapter will need to tell, and the documents would then be one part of that story.

Perhaps a way to address what I'm saying is that greater specificity will come as the writing groups begin to define their tasks and then could ask for whatever else might help as opposed to generically saying today, gee, can you find something more recent. So that would be another approach that I think might helpful to the purpose you described.

Jack?

DR. HENNINGFIELD: I have a couple of

observations that I'll make when we go back to general, but to go to your very specific question, I think we've already heard the industry challenge what we've been learning, and it would be very helpful for the industry, as quickly as possibly and as fully as possible, to give us what we've asked for; and very specifically, how much were they adding, when were they adding it, what was the rationale for adding it to menthol cigarettes branded as menthol as well as cigarettes that were not branded as menthol. It's just not credible that they were just doing it for the heck of it, especially in cigarettes not even branded as menthol.

So it would be very helpful if we're trying to evaluate what we've heard if the industry would tell us why they put it in and what their rationale was and how it fit with marketing. We've already asked them for that.

DR. SAMET: Corinne, do you want to chime in?

DR. HUSTEN: Let me just give you a

little update since you gave me the opening. Thank you, Jack.

So let me give you an update from my presentation this morning. I had said there was an incomplete submission from one company, and, in fact, yesterday on October 6th, we did receive a submission from this firm. We've been able to open the submission, and, in fact, the firm states that this submission contains the remaining responsive documents. This is hot off the press news. I wanted to let you know that the firms have now said that they've given us everything.

But I'd also like to clarify some things about Questions 11, 12, 13, 14 and 15 that may not have been completely clear. These five requests were voluntary. There are some health documents that we can require that the industry produce under 904(b). There are others that we can ask for, but they're not required to produce the documents even if they have them. And these particular questions do fall under the voluntary response.

I should also note that although industry health and research documents were not submitted specifically in response to these five questions, several companies did provide brief summaries or statements about the questions. Other companies specifically declined to respond to the request.

Now, for those brief summaries that we got, because those may include commercial confidential information or trade secret information, we'll make those responses available as appropriate that protects the confidentiality. So if, in fact, there's trade secret or commercial confidential information, we'll make that information available to the SGEs working on that matter.

DR. SAMET: Let me ask Drs. Yerger and Anderson one question. You submitted the draft documents, and it's noted that there's still work to be done, and I know, I'm sure, you've been working very hard to put these together. Perhaps either you or Corinne can define sort of the course of bringing these to a closure.

There's more writing to be done or sort of final drafts to be prepared?

DR. HUSTEN: Are you talking about the white papers?

DR. SAMET: The white papers, yes, the reviews.

DR. HUSTEN: Well, it is a continued work in progress in the sense that if we get more information, we'll be --

DR. SAMET: I'm sorry. I'm talking about the UCSF written reports.

DR. HUSTEN: The white papers that you were given were the scope of work of the initial request. So if you have additional things that you want, we'd need to go back and, again, see if there's researchers available or --

DR. SAMET: Okay. But those are final drafts, if you will, then?

DR. HUSTEN: Yes.

DR. SAMET: Okay. That wasn't clear.

Greg?

DR. CONNOLLY: Two points. One, if a

company figures out in 1985 how to produce a brake that works well, then there's no reason for them to go back in and refigure it out in 2005. We've seen a lot of suggestive evidence that when you look at it, it strongly suggests that well, maybe for beginner smokers that are youth and maybe black smokers, that menthol plays an important role in masking the effects of nicotine, and nicotine may be kept low. And then as they acclimate, we see alterations in the product. And we've seen a lot of suggestive evidence that those alterations affect chemosensory effects in three primary areas, olfaction, gustatory, but to a very less effect, and then tactile perception with nocireceptors. And even some saying that at very high dose, it looks like menthol can act like nicotine on impact and maybe control some behavior.

I think UCSF did an excellent job in what it was asked to do and what it was capable of doing, and I'm not criticizing it, and that is looking at the documents. But we do need to build

-- not so much going back and say to UCSF, we want you to become the Eckels expert on menthol in three months, because that's not going to happen.

But there are experts -- and I think I agree with Dan on this -- that know the current literature, and I think standard practice when Taubrig (ph) at WHO would meet with commission, an expert that could work with the subcommittee, they would take one specific topic and look at the current literature, in depth, what are the chemosensory effects. I think the NCI presentation on the nocireceptors and the trip receptors could have been stronger. I don't think the person really had the depth and the expertise in that area that some people have.

So that perhaps what we need to do is layer on top of this intent more substantive science from people who are experts, scientific expert, in these fields, so the committee then can synthesize this and see if what's being suggested here is actually scientifically valid.

DR. SAMET: Again, I'm going to reiterate

again that I think what you're describing is, at the next step, the task of the overall menthol report subcommittee and the particular writing groups to bring in that additional expertise. And I think, obviously, we need the science to be as deep as we can make it.

I think, Tim, probably the last comment before we close out this discussion.

DR. MCAFEE: Yes, this is just a quick specific possible request, which I'd be curious if we'd be interested in, which is basically, again, thinking about the fact that at least some of the industry actually did conduct some studies that were specifically looking at things like the relationship between menthol, nicotine and impact; that it would be nice not just to have rely on the documents, just like we're saying for the other types of the science, that it would be helpful to have made available whatever was done in terms of research that was done to try to understand this better by the industry.

DR. SAMET: Okay. Thank you.

So I'm going to suggest that we close this discussion and move to the open public hearing. I just want to suggest that it would probably not yet be useful to ask for any further sort of additional work on the documents until the writing subcommittee and its chapter groups come up with specifics that they might want to have explored in the documents. And, of course, the documents are also available online as a resource, and the committees themselves could look through it.

So I want to thank the UCSF group for your hard work, for coming, for sharing this with us, for taking a lot of tough questions and surviving. And we'll move on then to the open public hearing. So bear with me while I read what I need to say.

Open Public Hearing

Both the Food and Drug Administration, or FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open

public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process.

The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the Chair. Thank you for your cooperation.

So I think our first speaker is Dr. True from Lorillard.

DR. TRUE: Good afternoon. My name is Bill True. I'm the senior vice president of Research and Development for Lorillard Tobacco Company, and today I'm speaking on behalf of Lorillard. Before I begin my prepared comments, I think it's important to expand upon Dr. Husten's clarification of the companies' responsiveness to FDA's May 26th requests.

We believe that even with Dr. Husten's

clarification, there may be some impression that companies did not respond fully to Requests number 11 through 15. We believe this is clearly not the case. The May 26th requests were divided into two sections. The first section included Requests 1 through 10 and requested responses in the form of document productions. In contrast, the second section, which included Requests 11 through 15, were requests for background information. Although responses to Requests 1 through 10 were required, responses to Requests 11 through 15 were voluntary.

Lorillard, and my understanding, other major manufacturers, provided a substantial amount of information responsive to Requests 11 through 15. Lorillard went to great effort to provide the information responsive to these requests in a format most usable to the FDA.

If you examine the wording of the requests for 11 through 15, it is clear that providing explanations and summary data would be the most useful and appropriate response to these

requests. For example, in response to Requests 11 and 12, Lorillard provided graphs of the menthol and nicotine content of its cigarettes instead of providing thousands of quality control documents containing tens of thousands of data points. In addition, the companies provided a significant amount of information responsive to the requests in their submissions and presentations at the July 15th and 16th TPSAC meeting.

The current process does not allow sufficient interaction between FDA or TPSAC and the companies to clarify the information requested. In fact, it is my understanding that one company sought guidance and received no response.

Now, to address the white papers on industry documents presented earlier today. Lorillard remains committed to engage this committee and the FDA in discussion of any topic relevant to the scientific evaluation of menthol. However, we do not believe that an examination of a small selection of old internal business

documents can meaningfully contribute to TPSAC's work or to the new era of FDA regulation going forward.

Indeed, our preliminary review of the briefing materials reinforces our concern that documents of uncertain authorship considered outside of their chronological context, and in some instances improperly attributed to Lorillard, do not advance sound regulatory science. Lorillard will address specific assertions, discuss specific documents or comment on historical and contemporary practices at the appropriate time and in a manner that will advance FDA's regulatory science mandate regarding menthol.

I would, however, like to offer some general comments in order to remind the committee of some limitations inherent in the uses of small subset of historical documents selected from a larger document population. First, the documents selected provide little more than a mere glimpse of Lorillard's history. The dates of these

documents span several decades. In fact, most of the Lorillard documents referenced in the briefing materials are dated in the 1970s.

Over the decades both social and business environments change dramatically as did Lorillard's organization, policies, business practices and employees. Such a subset of selected documents cannot possibly place into accurate historical context the knowledge and actions of tens of thousands of Lorillard employees over a time period that spans at least five decades.

Lorillard does not constrain the creation of documents or free expression of the opinions of its employees whether or not they are consistent with Lorillard's principles or policies. As a result, individual documents may not be indicative of the beliefs of others in the organization and may not reflect company policy or management decisions and actions.

Second, historic documents, even if accurate at the time, may not be valid currently.

The current state of menthol science cannot be captured by reviewers of historic documents. The most recent research on menthol conducted by Lorillard was submitted to FDA and presented at previous TPSAC meetings and is also reflected in the documents produced to the FDA in April and August of 2010. This research was not incorporated into the briefing materials related today in the review of industry documents.

In addition, many historic marketing documents are irrelevant to current marketing practices, in large part due to Lorillard's agreement to limit the scope and nature of its product marketing and advertising in the 1998 Master Settlement Agreement. As a result of the MSA and other factors, historic documents regarding past marketing practices bear little resemblance to practices used today.

Third, given the over 800,000 Lorillard documents that are available on the Legacy website, the use of approximately 30 select Lorillard documents reviewed in the briefing

materials does not constitute a scientifically valid sampling by any measure. In fact, the authors of the document reviews also recognize the significant limitations of their conclusions due to the vast number of available documents from which they are to conduct their review in the time period given.

Some of the limitations highlighted by the authors include the short period of time for conducting the review required a strategic screening of the documents to be reviewed; context of the documents reviewed may have been lost and, therefore, the reviews cannot be comprehensive reports of all relevant documents; understanding the time period when the document was written, who wrote the document, why a document was written or why a study was performed requires extended time for reviewing and linking documents; and comparison of statistics gathered using different methodologies by different companies over several decades is difficult.

These limitations, among others, are not

simply disclaimers to read through quickly and dismiss. They significantly impact the validity of the conclusions that can be drawn from these reviews. Before TPSAC decides to rely on any of the document reviews, it is critically important for them to verify that the information represented to be in the documents is accurate, complete, considered in full context and meets applicable standards for quality, reliability and validity.

Just two weeks ago, this committee acknowledged that the menthol report subcommittee does not have the time to perform an encyclopedic summary and analysis of the large volume of available information on menthol. And yet again this morning, we heard a proposal to extend the deadline for this report. Couple that with the recognized limitations of these document reviews today as acknowledged by the authors, and the value of these reviews is seriously called into question.

Therefore, we must ask, is it proper to

use an incomplete assessment of industry documents as input into an admittedly incomplete analysis of all available scientific information on menthol? The use of a small set of selected Lorillard and other industry documents is inconsistent with a rigorous scientific process and certainly cannot establish any basis founded in science for TPSAC's recommendation regarding menthol and cigarettes.

Given that these historic documents have limited value in evaluating the science upon which the recommendation that TPSAC gives to the FDA must be based, this exercise has the danger of detracting from the important work that TPSAC must undertake. The committee should seek to employ an unbiased approach focused on sound regulatory science.

Lorillard believes that a cooperative dialogue and exchange with the FDA and TPSAC, focused on company research, data and documents related to the science of menthol and the development of menthol cigarettes, would be far more productive than further inquiry into outdated

documents.

Thank you very much.

DR. SAMET: Thank you. And just as a point of clarification, there was not a proposal for an extension of the deadline. I think you heard the opinion of one committee member. So I want to make --

DR. TRUE: I stand corrected.

DR. SAMET: I want to make that correction clear.

Questions from the committee? Jack?

DR. HENNINGFIELD: Do you agree with or dispute that menthol in cigarettes can make the smoke easier to inhale?

DR. TRUE: Dr. Henningfield, we had an extended discussion on smoking topography during our July 15th and July 16th session. Today, we're here to talk about the industry documents and the briefing reports, and that's what I'm prepared to talk about.

DR. HENNINGFIELD: That's one of the conclusions of the documents. And I'm just asking

if you agree or dispute that, because that came through from many documents over decades, and what seemed very persuasive to me. So I'm giving you the opportunity.

Do you agree with that conclusion --

DR. TRUE: I do not agree with that. I do not agree with that. I think you are seeing a number of quotes taken from individuals of varying backgrounds, of varying degrees, which have not been acknowledged in these presentations. We have no idea what their credentials are, whether they're a scientist, whether they're marketing individuals, whether they are real perceptions or that they're just -- real science behind them.

DR. HENNINGFIELD: Then why is menthol put in cigarettes, and why would it be put in cigarettes that are not even branded as menthol?

DR. SAMET: Why don't we stick to the topic at hand here?

Patricia?

DR. NEZ HENDERSON: Do you believe that the properties of menthol has changed over the

last 30, 40 years?

DR. TRUE: Have the properties of menthol changed?

DR. NEZ HENDERSON: Yes.

DR. TRUE: No, I don't believe the properties of menthol have changed over the last 40 years.

DR. NEZ HENDERSON: So, then, what has been given to us today is still the same?

DR. TRUE: The properties of menthol have remained unchanged.

DR. NEZ HENDERSON: Okay. Thank you.

DR. SAMET: Greg?

DR. TRUE: And a clarification also. Earlier, I believe that a comment about industry documents in terms of industry data on the marketing spend on African-American communities, that, to the best of our knowledge, although it was discussed at the July 15th and 16th meeting, I do not believe was ever formally requested to the companies. So I'd just like to make that clarification.

DR. CONNOLLY: Dr. True, thank you for your presentation. I'm going to ask a question. If you don't want to answer it, that's fine, but then I'm going to ask two questions about what you just presented.

The first question is, is it the position of the Lorillard Tobacco Company that nicotine is an addictive drug?

DR. TRUE: Nicotine is addictive.

DR. CONNOLLY: Okay. So does the Lorillard Tobacco Company sell a product containing the drug nicotine?

DR. TRUE: Lorillard Tobacco Company sells a product containing nicotine.

DR. CONNOLLY: So, in a sense, could I conclude then that Lorillard is selling a drug as an industry?

DR. TRUE: Lorillard is a consumer products company selling a tobacco product that consumers enjoy.

DR. CONNOLLY: But you just -- okay. You stated that since the MSA, you've dramatically

changed the marketing of menthol; is that correct?

DR. TRUE: That's correct.

DR. CONNOLLY: Since the MSA --

DR. TRUE: Excuse me. Since the MSA, we have corrected the marketing practices of all cigarettes.

DR. CONNOLLY: Okay. Thank you.

DR. TRUE: And our marketing practices of non-menthol and menthol cigarettes have been consistent over the years.

DR. CONNOLLY: Since the MSA, have you dramatically changed the menthol content of your cigarettes?

DR. TRUE: Absolutely not.

DR. CONNOLLY: Why so?

DR. TRUE: Because the level of menthol added to our cigarettes is the optimum taste balance between the strong premium tobacco taste signature we have and the amount of menthol that our consumers enjoy.

DR. CONNOLLY: Could you define the word "taste" for me?

DR. SAMET: Greg, actually, I'm going to suggest we're really focusing in on the documents now, and these comments are directed at the documents.

DR. CONNOLLY: Well, I just want to have it reflect in the record that menthol stated they've altered their marketing practices but they have not altered the menthol content of their cigarettes, and that's for the record.

DR. SAMET: Then I'll correct it to say that menthol didn't state, but I think Lorillard stated that.

Okay. I think other questions for Dr. True. Mark?

DR. CLANTON: I'm sort of struggling on how to formulate this question, so it'll probably be a little wacky. It's very clear, based on your presentation and other comments from industry, that we probably shouldn't look at this historical information because it's old and may not represent data that's driving current business decisions by the industry. I think that's a pretty clear theme

here.

The issue is when a business decision is made or a marketing decision is made, that decision in itself is not science. It's a decision. So it may be based on evidence. It may be based on science. It may be based on any number of things. So are you disputing somehow that the historical documents are not relevant because they weren't scientific or are you saying that they did not play a role in marketing and business decisions that were made by Lorillard or other companies?

DR. TRUE: The issues we have with the historical documents aren't the fact that they don't provide any potential useful information. I believe it's mostly the context, certainly from a marketing point of view, understanding the marketing practices of not only menthol but non-menthol cigarettes and other consumer product goods at that period of time and understanding who are the authors of these documents. Are they truly employees of the companies that they've been

attributed to or are they documents that have been received by outside marketing firms trying to gain business from the companies? And then the context of the document in terms of -- I believe the term was “lineage” that was provided by the briefing authors. Where did that document go? What was any follow-up action taken? I heard nothing this morning about the linkage between any of these opinions -- and, again, we don’t suppress our employees from having opinions -- those opinions and true management decisions that were ever made by any of these companies.

So that, to me, is the issue that I caution the committee on. It’s not the fact that there might not be some useful information in there. It’s not that the science in some cases has fundamentally changed. But it has evolved, and I think we need to look at it in the chronological context of what’s there.

DR. SAMET: Thank you. And I think the authors of these documents also iterated some of the concerns that you --

DR. TRUE: Exactly.

DR. SAMET: -- that you expressed.

I think we have a second speaker who we'll move to now. Thank you, Dr. True.

Our second speaker, who signed up today and has a more limited time, is from Altria. James Dillard.

MR. DILLARD: Good afternoon. Thank you, Dr. Samet, for granting me a couple minutes. I was not originally planning to speak today, but I appreciate Dr. Husten's clarification, which was really my concern after this morning. And I just wanted to sort of state a couple of positions from PM USA's perspective as it pertains to menthol and our responsiveness to the requests.

PM USA believes that we have been responsive to the request of May from the agency. And just as a reminder, we'd like to refresh the committee's memory that PM USA submitted a detailed analysis of the current scientific information concerning the use of menthol in cigarettes, and we did that in writing on June

30th and presented extensively at the July Tobacco Products Scientific Advisory Committee meeting.

On August 25th, we made our submission. It was over 3,600 documents consisting of interim and final reports, as well as other study documents and data. And PM USA believes that those submitted documents are quite responsive to, certainly, the requests of Questions 1 through 10.

There was also a discussion about Questions 11 through 16, and we also submitted information that was responsive to 11 through 16. And as an example, we submitted 5,500 individual data points that we believe we were responsive to Question 11 and 12 about menthol in cigarettes and menthol in smoke.

The only other point I wanted to make this afternoon is that we have also additionally voluntarily provided the data from the Total Exposure study that was discussed at the July meeting to the FDA, so the FDA is in possession of that. And I'd like to remind you that that particular study is probably the largest single

trial looking at cigarette smokers and biomarkers of potential harm and potential exposure, and some of those questions came up this afternoon.

So thank you, Dr. Samet, for allowing me a couple minutes to clarify PM USA.

DR. SAMET: Thank you, Mr. Dillard.

Are there questions? Greg?

DR. CONNOLLY: I'm just going to repeat the question. Since the MSA, have you changed your marketing of mentholated cigarettes in the consumer market? Have you changed your marketing practices based on the MSA?

MR. DILLARD: Since 1998, Dr. Connolly, yes, we have changed our marketing practices on both mentholated and non-mentholated cigarettes similarly, and we have also included some additional internal restrictions. So we've gone beyond the MSA.

DR. CONNOLLY: And have you changed the menthol content or properties in your cigarettes since signing the MSA?

MR. DILLARD: I would have the same

comment as Dr. True. No, we have been consistent.

DR. CONNOLLY: Thank you.

MR. DILLARD: Thank you.

DR. SAMET: Jack?

DR. HENNINGFIELD: Can you tell me if your documents dispute the conclusion that menthol can make it easier to inhale smoke?

MR. DILLARD: Well, I think looking back at the July meeting where that certainly did come up and there were topography studies in addition to our Total Exposure study work and other clinical work that we did, we believe that that work taken as a whole would dispute that. Yes, sir.

DR. HENNINGFIELD: So you do dispute that?

MR. DILLARD: I believe our work has been presented to the TPSAC in July.

DR. SAMET: Other clarifying questions? Tim?

DR. MCAFEE: Thanks. Mr. Dillard, there was a study that was presented by the UCSF group

that Philip Morris conducted back in the early 1990s, that looked at the nicotine effects on impact that varied based on menthol deliveries. So this apparently looks like you were looking at something that went far beyond the issue of improving flavor and even beyond the issue of it improving the ability to smoke, but actually going to the core of what people smoke for; impact.

So, could you comment on what the company's been doing since then in terms of acting on that information? Have you been -- how does this play into the ongoing role of menthol, the fact that it may actually be used to increase the effect of the acknowledged addictive ingredient, nicotine, in cigarettes?

MR. DILLARD: I think I can answer that one pretty easy. That goes back to when we were doing work on looking for a safer cigarette and the denicotinized cigarette. And so that was really specifically focused on that particular program, and once that program was shut down, that information hasn't been used since then. So it

was very specific to one particular program.

DR. CONNOLLY: Could you produce documents on Project ART? I know that wasn't asked by the committee, but could you do a production on Project ART, what you did, so we can have Dr. McAfee informed adequately of the research you did on ART? I think in the documents it's not -- there's no good collection of Project ART documents.

Could you produce that for the committee? Because I think that would be highly insightful and I think it would help Dr. McAfee quite a bit.

MR. DILLARD: I think certainly the response I've made before as well, that if the FDA requests particular information that they think would be helpful, we'll certainly take a look at that. Yes.

DR. SAMET: Thank you for your presentation.

MR. DILLARD: Thank you.

Committee Discussion

DR. SAMET: Just to conclude the open

public hearing session, the open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. Actually, I'm going to suggest that the committee will turn its attention to break and that we break till 3:30. So that's about 15 minutes from now. This is not a half-hour break. This is a 15-minute break.

(Whereupon, a recess was taken.)

DR. SAMET: Okay. So for those of the committee who are here and timely, let's talk over things that we need to do and talk about the time frame to get them done, with the possibility that we might finish today if we are efficient and effective.

So we, in my mind, have had an adequate discussion of the presentations on the documents and their potential use, and we are not returning to that topic. The framework that we discussed

this morning, the evidence classification and so on, I think we do need to go back to and have some further discussion as to whether, as presented or perhaps slightly modified, it is something we want to go with.

We want to look at a little bit about the writing subgroups and how they're going to proceed. There, we might have a little bit of discussion about what the chapters will look like in general. And again, I think a lot of this will become clearer as we begin our work. But I think there's some obvious points that we could make.

I think it would be premature for us to begin to talk about things like whether there are page limits, what the length will look like and so on because I think that we are just not there yet.

I think there are issues related to the logistics of developing the report that need to be discussed. And some of those relate, in fact, to getting the writing subgroups going so that as you scope your task and begin to fill in a more detailed outline, and think about who's on the

groups, whether additional expertise is going to be needed. Because if so -- and I think for some of the chapters, we really have already identified there will be -- in terms of process, it will be important to get that going.

So those are topics that at least between Karen, Corinne and myself, we think are important to cover.

Would there be other topics to put on the list?

[No response.]

DR. SAMET: Okay. In some time, about an hour, hour and a half from now, we're going to see where we are and make a decision about tomorrow, because there's a need to decide about logistics for tomorrow.

John?

DR. LAUTERBACH: Question on order. Are you saying that in terms of the white papers, we cannot ask any more questions or bring up information on those?

DR. SAMET: We've had quite a lengthy

discussion of the documents. I think if there are new issues that you want to surface briefly, then surface it. But, John, I think you've had your chance to provide input on what we heard from the UCSF reviews.

DR. LAUTERBACH: I just want to bring up one more point, that there is -- and this is in peer-reviewed literature, and I can give or send this to the committee or to Dr. Somers. But I hope everyone is familiar with what is known as the Alarie Test after President Yves Alarie at the University of Pittsburgh. There's information out there on menthol. Menthol is a fairly strong sensory irritant, and I can pass on the two peer-reviewed citations which include that.

DR. SAMET: That's fine. Just pass it along.

DR. LAUTERBACH: Okay.

DR. SAMET: All right. So what I think we might do is go back to the discussion of the framework. Again, I think we might go through these last three slides and see if there are

comments. And I think probably the more important issues relate to our approach to the peer-reviewed literature and my proposal that at least we begin with a systematic review process that has in part been done -- in the development of the white papers, we recognize that there are some articles that may have been missed. But that as the writing subgroups develop the evidence for their chapters, that this will not be, let's say, a review based in expert judgment and selection of articles, but at least one that has upfront a transparent description of how evidence was gathered and an attempt was made from the peer-reviewed literature to gather it systematically. And, in fact, this would be one obvious component of each chapter, which would be an explicit description of how evidence was gathered and evaluated, and that would fit within the methods section of each chapter.

So in this first item here, I'm committing us to begin with a systematic approach to the peer-reviewed literature. So we'll assume

that we're in agreement with that approach.

Greg, do you want to comment?

DR. CONNOLLY: I think this relates to the issues of resources. Is it expected for the subcommittee to do the work of looking at all the peer-reviewed literature or could we have FDA assist us with reaching out to that expert scientist who could do a first cut, then we can work with that expert scientist to synthesize? That's the first point.

DR. SAMET: Actually, let me respond to that, and Corinne may want to respond to that, too. I've had discussion, recognizing I think, as you well do and the committee does, that if you say systematic review, you're talking about a lot of work, and that the writing subgroups need to be staffed in some way. The mechanism would not be through FDA, as I understand it, per se, i.e., FDA staff, but it would be to identify a way to have people available to assist the writing subgroups. And I think we've had some discussions about how to do that.

Corinne, do you want to comment?

DR. HUSTEN: And I guess I distinguish the three types of help. One is if you feel you need an expert who has some expertise that the writing group doesn't have, something relevant to that chapter, please let us know as soon as possible because there are procedures we have to go through to get people. And if you wait too long, it may be hard for us to get them in time.

DR. CONNOLLY: We can do it tomorrow.

DR. HUSTEN: And second, we're looking at the ability to provide more -- I don't want to say grad student kind of support but sort of that kind of, you know, where if you need help with tables or reference, formatting, that type of stuff, and then the science writer can also help with just making sure there's consistency across the chapters in terms of the actual -- talking with authors individually about if there are things that can be done to help with the writing part of it.

Did that answer your question?

DR. SAMET: Yes. As a general comment, for example, the Agency for Healthcare Research and Quality funds I think it's now 15 evidence-based practice centers, the EPCs across the country. Those groups have in place sort of the professional staff who know how to carry out these reviews in a generic sense. And I think it's in a way that kind of capability that we would ideally have behind us, and I think that would serve us well not only for this report but other reports to come and to have some continuity. Many of us have done these kinds of reviews with graduate students, but the problem, of course, is that the graduate students move on and then you've lost that expertise. And it would be nice to have some continuity of expertise, in fact.

DR. HUSTEN: Well, and, in fact, that was probably a poor choice of terms because you can't use your own grad students because of the commercial confidential information, but what we are looking into is getting you contract support with folks who have the expertise to be able to do

some of that gathering for you.

DR. CONNOLLY: I just have one other comment. You have three slides you're looking at. And as I stated this morning, what Congress told us to do is recommendations. So there should be a fourth slide, a recommendation section with people assigned to look at recommendations, in my opinion, in the honor of a good close friend who passed away a year ago November, who helped this bill through. But, recommendations.

DR. SAMET: So, again, if you remember our draft outline, there is, of course, recommendations, and I view that as a job for all of the committee. And I've, of course, not anticipated how they might be framed, but, clearly, that's the bottom line.

Dorothy?

DR. HATSUKAMI: I would really find it very helpful to have some staff person go through some of the articles that have been cited in the white papers that were developed by the FDA because there are certain things are not included

in them, including the characteristics of the population, potential confounding factors, the sample size. And it would be very valuable to have that information to determine the strength of association as well as the consistency of the data and whether confounding factors had been examined.

DR. HUSTEN: The white papers were always intended to be this overview kind of big picture of what is out there in the literature in terms of how many studies and what they cover and things, and it was never intended to be the in-depth review of each article with all the things that you said. And that's where I think, one, we have been working to make all the articles available to the committee and subcommittee members. Obviously, articles are being added, and we've had some challenges about do we send you 30 CD ROMs or how do we get these to you in a format that's usable and efficient. But then again, I'm trying to get you this contract support in terms of what Jon was talking about in terms of evidence tables and sort of the details of the studies.

DR. SAMET: In the spirit of what Dorothy said, Corinne, you'll remember the database that we used for the 2004 and 2006 surgeon general's reports that had captured in a uniform way descriptors of studies, study populations, locations where they were carried out, all those factors controlled. That was, in fact, in that database, which the Office on Smoking and Health has not maintained. But the concept, I think it's exactly what you're saying. And, ideally, that information is there in a retrievable way so that you can look at it.

Greg?

DR. CONNOLLY: If we could leave having identified an expert -- I'm just hypothetically saying. If one wanted an expert on menthol and tobacco use, looking at population data, my mind just jumps to someone like Gary Giovino, if he'd be willing to come on board and have a contract and work and write. That's just very hypothetical because I don't know a process. But I think if we could leave feeling comfortable about who the

staff support would be, if there is an expert on abuse liability that knows thoroughly both the law and the literature, I think that could be helpful; if there's an expert on chemosensory effect that could look at the literature and give us a good synthesis.

If we could leave this meeting feeling comfortable with adequate staff support, so we're going to have -- I think we had four areas that we focused on -- it would make me feel a lot better that we're making progress.

DR. SAMET: So, again, the point, the support, the technical and writing support to the subgroups will not be FDA staff, but they will be these individuals who Corinne is seeking to identify the mechanism for bringing them on board, because the report has to be the work of TPSAC. So there's a distinction, just to emphasize.

I think the question of whether there are some people who we know would be valuable today, whose names could be listed, perhaps Gary or others, we might do that, but, also, I think the

writing subgroups will also need to do that.

Mark?

DR. CLANTON: Actually, this is a process question or a point. We've established subgroups for writing the report. So it would seem to me, unless it violates some principle of how we collect data or suggest expertise, that we've identified lead individuals for those sub or chapter groups. Shouldn't the offering -- if someone who's not on a group has an expert who they think would be valuable, can't we just have a direct process by which they offer up a name or two that is then vetted by the subgroup, and then a decision is made, or do we need the FDA to be sort of part of that process?

DR. HUSTEN: It's up to you to say who you want. It's up to us to figure out if we can get them for you.

DR. CLANTON: Well, that would be sort of the backend of the process issue. So if someone, an expert, was recommended to one of these groups and the group looked at it and says, yes, we need

that person, we'd have to come back to you anyway in order to work through the process of either making them a special government employee or whatever. But that would be the end part of the process.

I didn't know if we wanted to spend time necessarily here now vetting names, but we could probably work that through that other process.

DR. SAMET: Yes, one of our last items was to talk about logistics and we were going to go over exactly that process. I think a question -- I think probably Greg has put a different issue on the table, which is can we identify individuals here and now who we know we might want to assist the menthol subcommittee and ultimately TPSAC.

But I want to bring us back to the slide and get us through these three slides. And this discussion sort of began, remember, saying that we were going to do this peer-reviewed process, and then I think wandered into how we're going to get it done. And we will come back to that. But here we are committing ourselves to a process where we

will need support to get it done, either that or people are going to be working very hard and very long to put together this evidence.

We talked about the industry documents, and, again, I think it's probably going to sit with the subgroups on what comes next. We've seen the UCSF methodology for reviewing these, and UCSF and other groups, as Cathy pointed out, have looked at these documents. I think the last time I looked, there's hundreds, six, seven, 800 papers coming out of the documents.

Then the request to industry, another important source of information, we will be hearing about what has been found in those reviews. I think it will be in November?

DR. HUSTEN: As we get them, we'll bring them forward to the meetings. I can't predict exactly what we'll have when. They're all in progress.

DR. SAMET: Okay. And then the public input, of course, and that's come in various forms of submissions.

So let's go to the next -- yes?

DR. HATSUKAMI: In terms of the requests from the industry, there was some really important information that was presented at our last TPSAC meeting. But in order to do a really good review of that information, we would need to know more specifics, very similar to the peer-reviewed literature, in terms of the population that was studied and the characteristics, the controlling confounding factors.

I know that that was discussed in the presentations, but I'm not really sure whether we have written documents other than the ones that were provided to the TPSAC members, you know, describing the studies that were presented at the --

DR. HUSTEN: There were background materials that the industry --

DR. HATSUKAMI: Right, I saw that.

DR. HUSTEN: -- submitted that I think had more detailed discussion than what was presented. Whether it has everything you want, I

don’t know, but they were more detailed.

DR. SAMET: So, Dorothy, perhaps again, this is something that would come out of the writing subgroups. If additional information is needed as you go through the submissions and the attached background, as whether that’s more detailed information on population selection, characteristics, I would assume that we could make those requests to the industry for that additional information to really make the evidence submitted more valuable.

DR. CONNOLLY: I just have an observation. I asked a previous presenter are you a drug industry or are you a consumer product industry. And the response was I’m a consumer product industry. Well, consumer product groups, when they market a product, really look at the market response and not the science base as a drug industry does.

So we’re going to get information from the industry, and I would hope that as a group in working with the industry in this legislation over

time, we can have the industry become to recognize that it is a drug. We've acknowledged that. We're selling a drug in this product, and we're moving from being a consumer product industry to more of a regulated industry as a drug industry.

I'm fearful that we're going to get a lot of documents that are not going to be necessarily scientific. They're going to be reflecting of how a consumer product industry behaves, and that is going to complicate the process of synthesizing science. It's not going to have like SmithKline walking before us and giving us biomarkers of exposure and talking about abuse liability and so on and so forth. So we have to recognize that and just understand that, and put that in our equation of weighing the science.

DR. SAMET: Okay. I'm going to the second slide. So this, again, said I think a few things. And just, again, we're going to -- in terms of sort of adopting principles that we will be following, and this will go into what is the introductory sort of Chapter 1-2 of our report.

The target inference, and, again, this is where we sometimes might be looking for causal relationships, sometimes we'll be looking at associations. And I think, again, that there was some flexibility, and I just want to make clear that our task is, let's say, not like of a surgeon general's report on causation of disease where there's a single target. We're really dealing with a system, if you will, in the broadest sense, and there are aspects of it we're trying to understand to improve public health.

The criteria for evaluation, again, the criteria for evaluation as spelled out. And, again, this goes back to I think was Corinne's statement, that while we would like not to see just from the committee a statement that this is evidence that is more likely than not, but she would like an explanation. And I think part of that explanation would lie in the judgment of the writing subgroups, the subcommittee, and ultimately of TPSAC itself as to the strength of the evidence measured by these or if there are

other relevant features that might be brought in. For some of the issues of concern, there might well be experimental data of different sorts, clinical trials.

So there will be a variety of types of data that we would want to, in a sense, march through in an organized way as we describe the strength of evidence, the proposal here that's sort of, in essence, is a restatement of the standard sort of weight of evidence. And then the classification scheme, which sits on the next slide, and we'll spend some time on that.

So let's see if there's comments at this point. I think the job of those of us involved in Chapters 1 and 2 will be turning this into words.

Slide 3, imagine that, three slides. Okay. So, again, this was the proposal for how we would classify the sort of the bottom lines of the reviews of the evidence related to the various questions; that we were going to use the balancing point, this equipoise point; that there's a category above equipoise, at equipoise, below

equipoise -- which I think I'm still bothered by the wording of that third one because I think it captures the balance point, but I'll juggle it -- and then this insufficient evidence, that this classification we think could be a useful one for decision-making. It also could be useful for identifying those points of uncertainty at which research could make a difference.

So, again, let me offer a suggestion here.

Okay. Questions here? Mark?

DR. CLANTON: I think the concept of equipoise fits the state of the data and the state of the science, so this idea of creating a balancing act around the data and then specifying what we think about it makes perfect sense. Also, the issue that was brought up by Greg earlier about the statutory language of likelihood, going back to that word that appears in the statute, is well covered by the concept of equipoise, so I would certainly be in favor of using the concept.

DR. SAMET: Greg?

DR. CONNOLLY: This model, it's from an -- I think you began with the EPA and then you switched over to the BA issues. But we were looking at a very specific -- with the EPA case, let's say we're looking at very specific compounds. So our evidence is going to focus on the compound. The difficulty we seem to have is that we are -- when we look at menthol, we're looking at a variety of effects, both within the product design, the chemosensory activities, the population of effects.

So there has to be interrelatedness and interrelationships between the bodies of evidence to allow equipoise to work in this particular environment. That arena is a much more difficult challenge than looking at a single constituent. It's almost like saying, well, I'm going to make a causal assessment on cigarette smoke when we have a very complex mixture of 5,000 compounds and we throw our hands up. We have to think about interrelationships and interdependence of different types of evidence to arrive at

conclusions.

DR. SAMET: I think your point is important, and I think goes back to some discussion we had this morning when we talked about Chapter 6, which is the public health impact chapter, how you put this together. I think here we're laying out the approach that would be used to answering the specific questions and lining it up. And I agree that -- and, again, I use the word "system," and that's sort of where you're coming back to. There are multiple points of interaction that range from pharmacological effects to marketing, to culture, to many, many different factors that in the end influence the public health consequences of having menthol cigarettes on the market.

Tim?

DR. MCAFEE: I would maybe expand on that a little bit. I think this is going to work great for kind of the classic is there an association or isn't there an association question. The challenge will be that to the extent to which Greg

is right, that the committee is being asked to do something more by Congress and perhaps by FDA, which is to actually make a recommendation for what should be done about the presence of nicotine in cigarettes going on into the future. It seems to me that there's got to be some more stuff that really is related to even things like the weight of -- because it may be that, otherwise, months from now we will have agonized and reviewed a lot of stuff, but, basically, fundamentally, it will come down to, well, it doesn't -- so what, it doesn't matter whether it's thumbs up or thumbs down on this; we'd still want to take it out or we'd still want -- it wouldn't matter anyway.

So it's like would it at some point be helpful to make a kind of decision tree analysis around what are the key elements where we actually would make a decision yea or nay, and then particularly focus on those elements. And if we know it's not critical to that -- again, we'd need to answer the question because FDA needs an answer to that question. But we would understand a

priori what the decision making process would be around the policy decision at the end of the road.

DR. CONNOLLY: Can I just add? When I say “recommendation,” I don’t think of yea or nay, and I think we have multiple options as a policy entity, as a body making a recommendation to look at options. And I think that is worthy of discourse and time. And I think the public is under this perception yea or nay. And it may be yea or nay. But I don’t think we should lock ourselves in necessarily. We may have process issues that come before us; well, this is just insufficient evidence here. So that relates to one option, and that’s a process issue that’s recommended; or there may be sufficient evidence here, and that relates to a much different directive option.

Carpenter’s book on FDA, which I highly recommend to everyone, he talks about authority as being directive. He also talks about authority as being a gatekeeper function, and then authority being influence of the process that you establish.

And I think we can learn from that. I'll get everyone the reference to the Carpenter book. I'm just becoming enamored by his writings.

DR. MCAFEE: Can I make a quick response to that?

DR. SAMET: Yes. Actually, before you do, I just wanted to respond to you in part. Again, the key here is developing the evidence base for any decision making and providing the scientific guidance around developing that evidence base. I see that, in the end, there are probably going to need to be some decision-making tools, model-based tools, that are going to be useful for TPSAC and for FDA in putting all the information together. Because you're right, in the end there are going to be some recommendations that overarch any of these individual bodies of evidence that we are going to evaluate and reach conclusions. And as I've said before, we're looking at some of the different building blocks towards that overall decision in setting out the scientific basis for decision-making.

So I think we're the Tobacco Products Scientific Advisory Committee, not the tobacco products policy advisory committee, and I think that's clearly an important distinction to keep in mind.

Let's see. Jack?

DR. HENNINGFIELD: I think part of what we're struggling with is a typical advisory committee would have a very simple question that's a yes/no at the end of the day. Most of us have served on those committees. Most of us have also contributed to surgeon general's reports that are extremely exhaustive. And I think we've got to draw the line in a reasonable and achievable place and not get bogged down in trying to produce a surgeon general's report, because we can't, and I don't think we have to render an opinion on the key questions that are before us. We don't have to understand all of the mechanisms of action. There will be many things we don't understand, but we can still come to certain conclusions whether or not we understand I think as long as we

articulate what we don't know, what the basis was.

But what would be helpful is what should the end product look like; is there a good model that we should be shooting for. And I suggest that it not be a surgeon general's report model or we will never get there.

DR. SAMET: Right. Jack, I think, is one of the few TPSAC members who's not on the subcommittee. We had a little bit of that discussion a week ago, and we expressed clearly that this should not be a surgeon general's report. For one, it would never be done by March unless you made it 2000 and whatever. Sorry, Tim.

But that's clearly not the goal. And I think the kind of evaluative kinds of things, for example, that you see from the Institute of Medicine that are not this thick but more constrained, are in my mind what we have as a goal. Now, that's not to say there couldn't be lots of tables that are in appendixes or put on the Web, but I think we want something that really does synthesize.

I think one point, again, is that we don't yet have -- let's say or FDA does not have in place, or advisory committee, sort of modelers who might take the different pieces we're putting together and develop the overall model for population impact, and that's a tool that will be needed along the way, I think, for sure.

Tim, did you want to -- you're okay. Cathy?

DR. BACKINGER: I'm not quite sure how to ask this, but I missed the very first TPSAC meeting when you first met around this topic. And so, at least on this piece of paper, there's eight questions, and then you showed earlier the different writing groups. But I'm assuming that the writing committee has some leeway in deciding the relative weight of importance.

So this kind of gets back to how are you defining impact on the public health. All eight of these questions, for example, each of the different writing subcommittees are going to be weighting things all equally or will there be -- I

mean, at some point there will need to be a discussion about, well, is initiation really the key here and, therefore, marketing and initiation, is that more important than the toxicological effects?

DR. SAMET: And I think that's where, if we had the sort of overall integrative models, it would be very valuable, exactly, to answer that question. Absent such models, I think there will have to be discussions among the full menthol subcommittee that will do this relative weighting and evaluation, based on their judgment and whatever other tools they may have in hand. But I think you're absolutely correct.

DR. CONNOLLY: I would just say in anything we do, we just start off by what the law says, one, two, three, risks and benefits, increased likelihood of use, decreased likelihood of quitting. Those are our three questions, and we've got to answer one, two, three. If we can answer all three, answer one or two, and then we come back and -- you know, this is what the law

told us to do. And then based on --

DR. SAMET: There is no doubt that that will be in Chapter 1.

DR. CONNOLLY: Front page.

DR. SAMET: Okay.

Mark, did you have comments?

DR. CLANTON: No.

DR. SAMET: Let's see. Other comments? So, again, what I would like to do is have enough discussion to be confident that if the Chapter 1, 2 subgroup essentially quickly writes this up to get us started, that -- this is not a voting matter, but just one where I want to make sure that there's agreement that this is a reasonable starting point.

Yes, Dorothy?

DR. HATSUKAMI: Just to go over this classification scheme, evidence that's suggestive but not sufficient, where would that fit? Would it be under the second --

DR. SAMET: That would be in -- it would be evidence is insufficient to conclude that a

relationship is more likely than not. So that's below the equipoise point, so that would correspond, yes.

DR. CONNOLLY: Jon, to get back to my point about interdependence and interrelationships between the different sets of data, now, you could have four chapters that come up with, well, suggestive, suggestive, suggestive, but then when one takes a step back and collapses that data, all of a sudden suggestive could take on a whole different meaning, and somehow that model has to reflect that. I think what we heard today from the UCSF demonstrates intent. That does a very good job, but does it satisfy the science that we want to be examining?

If we add to that prevalence data from a population, we add to that knowledge of chemosensory effect, then what we have is -- then suggestive, maybe by being interrelated, interdependent, satisfies the equipoise model.

DR. SAMET: Yes, so I think we've sort of gone the same track as I think what Cathy was

talking about, and this is sort of how do we put Humpty Dumpty back together again, if you will. And I think, in my mind, the ideal tool for that would be the right models that correspond to the rough diagram I've provided in that note or something like that where you -- and ideally, you would have enough information to estimate some of the model parameters or reasonable basis for describing them.

I think we'll have to see how far along we get. And again, absent that, I think I share the agreement -- I'm in agreement with everybody who's saying that there's overall synthesis that has to take place to fulfill our requirements.

So I think next step on this will be to get something in writing. I think our Chapter 1 or 2 introduction can probably best be written right away and sort of provide a logic roadmap for moving forward.

So any other thoughts on this?

[No response.]

DR. SAMET: Okay. Then maybe we should

go and talk a little bit about the writing subgroups. So again, here just we've run through these quickly. I think in terms of logistics, there will need to be meetings of the subgroups by phone to get organized, and I think ideally those will happen quickly. I think we can talk a little bit about schedule. But I think particularly around the issues of either additional experts that might be needed or additional data to be requested, we'll have to move I think quickly here.

If you remember, I think the first person is the leader in every case, so you know who you are. Is there a chance to put Benowitz in front of all of them?

[Laughter.]

DR. CONNOLLY: Yes.

DR. SAMET: And maybe a little bit of discussion at this point about what chapters might look like. And, again, we haven't had a chance to sort of frame this yet, but I think, again, the introduction would have to bound what the topic is

and say what the questions are to be answered. There would need to be a description of the methods, the approach for finding and evaluating the evidence, and then a laying out of the results, and we can talk about some ways to do that. And then, finally, of course, conclusions and discussion leading to those conclusions.

So just thoughts about the structure of chapters generically? I think we've all done this kind of thing. So we're going to add a slide here, and we'll just capture whatever wisdom we might have. So let's call this generic outline. So our generic outline is going to have an introduction, but I think here there needs to be a very explicit statement of what are the questions that are being addressed, what is the topic. And we probably should do this in the same way in each chapter. I think that's where this report will be addressed. And then, let's do methods next, and then we'll come back and just look at our work here.

So here, explicit description of evidence

gathering approach. And then under that, a explicit description of the evidence evaluation method, and that is whether it's experimental design, methods of measurement, the different ways to look at the quality of the study, whether it's a trial or observation or experimental.

Then there's the presentation of the results. And I think one decision here is -- and this goes back to the surgeon general report or not. For those of you who know the surgeon general's reports well, probably most people in the room, they contain these voluminous tables that describe the evidence. I think we need -- why don't we put evidence tables under presentation of results, but I don't know that these necessarily need to be voluminous or in the body of the report.

I don't know. Corinne, I don't know whether you have comments about sort of posting materials on the Web or archiving them and not putting them into the report, per se. I'm not sure I know. Is this going to be a sort of hard

copy document? Is it going to -- what's it going to look like?

DR. HUSTEN: I think the main thing is the documents have to go through the DFO and then back out to committee members. So people can work on their work electronically, working with --

DR. SAMET: I'm actually thinking about the final product. In other words, for example, if we have 200 pages of text but there are 500 pages of tables that we don't necessary want caught up in the report but want to archive somewhere, for example.

DR. HUSTEN: I think you can get them to us however you want to get them to us. This is a open process in terms of the final report, so whatever is produced will get posted.

DR. SAMET: Okay. And, again, continuing the generic outline, we present the evidence. We clearly have to go through the strengths and limitations in some fashion. And, again, I think this is where the chapters will have to be individual. If there are two or three key

studies, that would be presented. But, certainly, strengths and limitations of key studies would be reviewed.

Let's just call the next section, which will be a major -- yes. we'll just call that synthesis, evidence synthesis. So there we would have a discussion of the evidence by the criteria. I think a statement, a classification of the evidence, that's our four-level classification. And then I think, after that, a discussion of the implications of the evidence. And then maybe if one of those implications could be research needs or we could put research needs as a separate -- and research needs, that would be fine.

So there's a generic outline. Again, it's a starting point. Comments or thoughts? It seems to me that's generic enough to fit, but it has to fit this kind of approach. Remember, we're trying to fit a lot of different topics with something that ought to at least look the same, I think, from topic to topic.

Greg?

DR. CONNOLLY: Jon, on the evidence synthesis, would you see in that section a synthesis between other sections of the report or do you see this is a freestanding endeavor for that particular topic area?

DR. SAMET: So, the best answer is I don't know. I think if in approaching one of the topic's chapters there are important interactions that are found with factors in other topics, I think they should be brought out here, and then again in the overall -- in our modeling -- in our overall impact chapter, it would be brought out.

Mark?

DR. CLANTON: So back to the question of do we want to have a last section that says conclusions and/or recommendations for each chapter or is this something we want to sort of offer up, each writing group offers up to some final set of recommendations. What is your pleasure on --

DR. SAMET: Again, I'm not sure I have one, and I think we'll have to see how this works

out. I could see that we at the end of each chapter might appropriately discuss research needs related to a topic of that chapter. Again, as we come back to pull things together, we might talk about the overarching needs and what is there. I think we'll just have to see how this goes.

DR. CLANTON: I think along those lines maybe we should then just proceed with in the writing that we should offer up either conclusions and/or recommendations in our draft and then make a decision about where that goes or whether those statements are appropriate or not.

DR. SAMET: Tim?

DR. MCAFEE: This looks great. Just one slight suggestion that perhaps part of the introduction ought to explicitly be that the significance of the question -- you're hitting the implications at the end, but essentially a brief statement as to why we're asking this question and how it ties in with the larger picture.

DR. SAMET: That's helpful.

DR. CONNOLLY: Jon, is there a model

anywhere that we're going to reference for looking at this issue of menthol as it relates to what the definition is of an impact on public health? Are we going to have a model that would give us a grounding then to go into a chapter?

DR. SAMET: So let me ask first if you have something in mind or you're just throwing out the idea?

DR. CONNOLLY: I think at our first meeting, we spent quite a bit of time discussing questions to industry, and it seemed to fall into four general areas that linked sequentially. And perhaps we could get the register or get what we developed at the first meeting tomorrow. That, to me, provided a pretty good model for looking at the linkages of the questions we were asking. It was different than I think a traditional approach to a particular constituent, let's say, in a EPA model, but it was more of a model that looked at a product, its impact on an individual, the mechanisms for such, and then the population effect.

I don't think we're being instructed by Congress to have at that model disease and death at the end. This is a different -- this is a really departure from a traditional FDA function, where now we're looking at population, which would be talking about initiation, cessation as the endpoint in the model.

DR. SAMET: One of the endpoints.

DR. CONNOLLY: One of the endpoints.

DR. SAMET: I think there are multiples of concerns. I was thinking that some of the attempts to think about this kind of model -- Cathy, I was thinking about your NCI might work in sort of the systems monograph.

Do you want to mention that?

DR. BACKINGER: As far as the structure?

DR. SAMET: Well, just in terms of what was done, and that's, in part, laying out some of the general approaches that could be used and applying them to tobacco. And there's some extensive frameworks within those chapters.

DR. BACKINGER: Right, and I think that's

what I was maybe perhaps getting at earlier, which is kind of the different weight, because some of the frameworks had -- the different inputs and outputs were weighted differently, depending on the evidence. But I guess, Jon, I'm not really quite sure what you're asking as far as laying out the monograph with regards to this.

DR. SAMET: Well, I was actually trying to explore whether there was anything in particular we could point to in response to Greg's question.

DR. CONNOLLY: I think Volume 13, when it looked at light cigarettes, had a hard time drawing a conclusion in any one given chapter, but when Volume 13 consolidated those different chapters, it drew conclusions.

DR. BACKINGER: Right. And that was a separate chapter at the end, right, with summary and conclusions that then kind of brought together the conclusions of each chapter to come up with the final conclusions. You're right. So it was kind of that the sum was more than the total of

the parts.

DR. CONNOLLY: In a sense, it's similar to this. You had a section on marketing.

DR. BACKINGER: Right.

DR. CONNOLLY: You had a section on topography. You had a section on health outcomes. You had a section on prevalence and use. And I don't think -- any one section couldn't stand on its own to respond to what Volume 13 was answering.

DR. BACKINGER: Right. So I think you could have in each chapter the conclusions, but then you'd want to have a separate group that comes up with putting all the conclusions --

DR. SAMET: Well, that's all of it, and that is the way the outline is structured right now.

DR. BACKINGER: Okay.

DR. SAMET: I think overlaying this would be at least some -- our best general ideas in the "model or framework" of how these factors relate to one another. And I think there's something I

provided in our subcommittee that starts down that track.

DR. CONNOLLY: Well, Jon, the more I think about it, the more I think Volume 13 addressed one aspect of design of a cigarette product, and then it walked through that aspect in terms of how was it designed, how was it marketed, how was it used within a population, and then, in this case, it dealt with health effects on the epidemiology. I don't think we're necessarily going to make a conclusion. I don't know. But we could learn from Volume 13. It wasn't a surgeon general's report. It was authored by experts in particular areas, and I think it mirrors what we're trying to think about here in many respects. It's worth going back and looking at.

DR. BACKINGER: All of the monographs are up on the NCI website, so it's easy to just look at the chapter outlines for each of them and see how those were constructed.

DR. SAMET: I think our task is like many that involves bring together many, many different

lines of information to reach some overall conclusions. And for those of you who aren't familiar with the NCI monograph series -- probably everybody is. I think you're up to number 20.

DR. BACKINGER: We've published 20 now.

DR. SAMET: Now. Some of them provide useful examples. Monograph 13, for example, of approaching, that was one aspect of tobacco products, cigarettes, as Greg mentioned.

Okay. So generic outline, further comments? We just need to fill them all in now.

DR. CONNOLLY: Jon, one issue that intrigues me is the whole issue of equity that really goes into, okay, do the marketing practices reflect equity and justice for target groups. And we heard statements last week that we don't target blacks. But it goes a little bit beyond science, but it is part of science. And that is, we as a nation have an obligation to examine issues of equity within our populations and we have to examine the health of high-risk groups. And I just don't know how or where that goes, if that

goes with a part of a discussion of use by African-Americans.

I think, again, we're being asked to do science, but also we are a body that has to be grounded in issues for justice for Americans and has injustice been -- or has the marketing been inequitable, and has it resulted in --

DR. SAMET: So just as a reminder, I think that will be up front because it's part of our responsibility. And, again, in the writing subgroup, I think the subcommittee had discussions about the handling of this topic which does appear. So I think we will be there. We need to make sure we are.

Mark?

DR. CLANTON: For those people who aren't part of the menthol report writing group, there was a larger discussion about whether or not special populations, particularly African-Americans, should be addressed throughout all of the sections and chapters. And at least for this first draft, we concluded that it would become a

substantial part of the discussion on the public health impact of menthol. So I just wanted to share that with everybody, that we did discuss whether there should be crosscutting or be featured there, and for right now, it's featured in number 7.

So, Greg, discussions related to marketing, equity, public health impact could find their way to Section 7 or Chapter 7.

DR. CONNOLLY: I think part of that, too -- and I don't want to go beyond the scope of a scientific committee, but there are issues of justice that the public expects to be addressed and how the lack of justice and inequality affects public health. It's intimately related. Issues of disparity in this nation are the predictors of poor public health. And so in this section here, you may conceivably have someone assist in weaving in concepts of equity and I think it goes back to marketing.

DR. SAMET: Yes, I think the group will be there. I'm going to suggest that we move to

discussion of some of the logistics.

Corinne, do you want to comment here perhaps?

DR. HUSTEN: I think it would just help us to have a clearer understanding of what kind of support you're going to need. We've talked about expert consultants who have specific expertise that could be helpful, but then I'm talking more about the general support in terms of writing the chapter, how many people are we talking, what sort of level of expertise, because we just have to be able to plan and obtain that help. And so, if I could get a little more clarity about what you want, that would probably help us.

DR. SAMET: So I think just to remind the committee of what we have, we do have our writer who will assist with the style, getting things correct, making sure that there's more or less a common voice across the document and so on, deal with the kinds of inconsistencies that often take a lot of work to fix. And maybe one of the things we might ask her to do early on, and perhaps just

make a note of this, is to put together a style sheet for us on how we're going to handle certain things and phrases. I think if we started on a common framework, that would be helpful for efficiency. So we should probably have a discussion about that. That's a pretty nitty-gritty issue.

I think there's this need, which you've heard from me before and I think heard re-expressed by the committee, that the writing subgroups will need sort of what I'll call for the moment research assistant kind of support. And I think absent that, I think we'll be slowed and far less efficient, and it will be time consuming. So I know you're working on that support as well.

DR. HUSTEN: But this is where I think it would be helpful, how many do you need, what sort of -- do you want master's level, PhD level? Give me a little bit of context about what you're looking for.

DR. SAMET: So I will make the suggestion that, ideally, these would be individuals who are

the master's level and have some skill in sort of data management, synthesis, building tables, the ability to look at a technical paper and abstract the information if given a template for doing so. So I think, ideally, such individuals are probably at the master's level.

DR. CONNOLLY: I would argue on certain sections that may be true. On certain sections, given the absence of previous work in a very specific scientific field, that we may want to get a PhD. I could say, if I want to talk about contraband, the name that comes to my mind is Luk Joossens. He studied contraband for ten years.

DR. SAMET: Greg, actually you're -- I'm talking about the technical support to get the job done.

DR. CONNOLLY: I'm sorry.

DR. SAMET: And not the scientific expertise. We don't need Luk to make the tables, but I think at the level of sort of just providing assistance. But the other question you asked was how many, and I'm not sure I know a number. Of

course, the right answer is enough. And if you had a mechanism in place that was somewhat flexible -- of course, the problem is that we'll be in a flurry of activity, and that's the kind of point where enough is really what we'll need, and I'm not sure I know how many that is.

So you might think about that as you think about the mechanism to provide the support. So, ideally, some sort of group that has some sort of flexibility. And if it's three FTEs, then that's going to drop in a couple of months to one FTE, then they can do that. Ideally, these would be people who come in with some generic knowledge.

John?

DR. LAUTERBACH: What sort of support do Mr. Hamm and myself get for helping writing our part of the report? I don't have an extensive staff of post-docs, graduate students, access to a library, et cetera?

DR. SAMET: Well, I'm not sure most of us have sort of, if you will, graduate students, or whatever, sitting to just do our bidding. So I

have to make that correction. Life is not like that.

DR. CONNOLLY: John, the big bucks are with the industry, not with us.

DR. LAUTERBACH: But Dr. Connolly --

DR. SAMET: Let me answer your question. I don't know, and I think Corinne has to respond to this, about support for the development of the chapter, the industry perspectives document.

DR. HUSTEN: I think you need to let us know what you need. It's an industry perspective. You represent your constituents. So I don't know if you expect that you personally will be writing every word or you'll be consulting with the folks you represent for some assistance. If you need help, let us know what you need.

DR. SAMET: Dan?

DR. HECK: If I might comment briefly on that, we did have a conference call among at least the larger companies this past week that have the largest staffs, and we're still working towards deciding how exactly to address this directive or

suggestion that we prepare a separate report. So I don't -- I will say that I think our intention will be to follow the same chapter headings to make it useful as possible to the process, to meet the requirement for stakeholder participation.

We can maybe even talk later about the specifics of how is that done, is there an industry stakeholder section in each chapter or is that going to be a freestanding work. We can figure that out later. But we are still developing a sense of our needs and the magnitude of the effort which is considerable for us as well, believe me.

DR. SAMET: Well, I think, John, as this industry perspective planning continues, if there's need to turn to FDA to understand how this will be supported, I think you'll turn to Corinne and ask, I think is the answer to the question.

Jack? No.

Okay. Let's see. So back to logistics.

Do you have other comments? We need to have calls. So the other support, the input from

topic-specific experts, need to be determined early. So that's where Luk or somebody else would figure in.

Other comments about logistics? Karen? Corinne?

DR. CONNOLLY: Just on meetings and constraints of the statute, public transparency, are we going to have enough time to get groups together and meet the FDAAA Act and be transparent? I'm just a little concerned about process issues the way I've seen the committee operate.

DR. HUSTEN: I guess I'm not completely clear what the question is. The idea is that, as we had said, there'd be these small workgroups. If you need outside experts, because there's no one on the workgroup who really has the particular area of expertise --

DR. CONNOLLY: The small groups are not constrained by the FDAAA Act? It doesn't have to be transparent in a public meeting? No, okay.

DR. HUSTEN: Because they may be

reviewing commercial confidential information, those will be closed, but the DFO has to participate in all calls to make sure that the group is complying with all parts of the statute.

DR. CONNOLLY: Maybe to industry, Dan, you could answer. Can we expect any challenges by the industry in terms of proprietary information and sharing it with members of the committee?

DR. HUSTEN: Let me clarify. The trade secret and commercial confidential information that you might receive has to stay confidential. So you can review it, but you cannot reveal it in the report or in any discussion to the committee. So you'll need to figure out how you do that in terms of being able to utilize it, but you cannot bring forward confidential or trade secret information, either in the written report or in the open meetings.

DR. CONNOLLY: I spent six years in federal court over this very specific issue, on ingredients, and I just want to know, a month from now, we don't see a court -- I'm just asking are

we going to see a court challenge or are we protected under the FDAAA Act from court challenges if proprietary information is shared with committee members.

DR. SAMET: I'm not sure that that question has an answer from anybody around the table.

Karen?

DR. TEMPLETON-SOMERS: Any confidential information that a subcommittee reviews and decides needs to be included will be presented in a public meeting after appropriate redactions and review for confidential. If it's a particular company, they would be consulted before that was released.

DR. SAMET: Okay. So we've covered a lot of ground even though it is day one.

Dorothy?

DR. HATSUKAMI: I just have a logistic question regarding our little subcommittee calls. Do we have to go through the FDA to make those calls?

[Dr. Husten gestures yes.]

DR. HATSUKAMI: Okay. So I just can't call Mark up and say hey.

DR. HUSTEN: The DFO needs to be participating in all those calls.

DR. SAMET: Mark?

DR. CLANTON: So along those lines, we really should leave today knowing who our contact should be. So in terms of setting up conference calls, deciding if we need a researcher or scientific writer, all of that is going to the DFO, who may change --

DR. TEMPLETON-SOMERS: Use the e-mail, tpsac@fda.hhs.gov and you'll reach the entire TPSAC team. It may not be the DFO for everyone, depending on how many of you want to meet at the same time, but one of us.

DR. SAMET: Okay. And, again, a first task will be to convene those first writing subgroup meetings.

So I was about to say that it's quarter of 5:00 on day one of our meeting. We're running

till 6:00. I am sensing that we may -- there's nothing wrong with getting our job done earlier, but that's a question or a yes. Two thumbs up. In fact, every time I leave a meeting early or an airplane lands early, I feel like my life has been extended.

[Laughter.]

DR. SAMET: So I wonder if there's other business that we need to do. We need to make a determination for, one, as to whether there is any need to meet tomorrow, and I don't think there is. I actually feel like we've done what we needed to do. We've heard a lot of information from the UCSF. We've had an ample opportunity to discuss it. I think we've taken the guideline framework discussion far enough to know that we will move forward and use it. We have a starting point.

I think all the groups have heard about the process for moving forward with the writing. We know the timetable. And we have some general ideas about the model. I think now we need to sort of get started, and I think as we move forward,

there will undoubtedly be a lot of questions to answer.

So let me just make -- first of all, can we agree that we probably don't need to be sitting here tomorrow at 8:00?

[Members affirm.]

DR. SAMET: Okay. All right. Is that unanimous?

Greg? Just checking.

DR. CONNOLLY: I don't want to hurt John's feelings. That's all.

DR. SAMET: And then while we're here, though, other things that we could or should discuss.

Yes, Dorothy?

DR. HATSUKAMI: Yes. One of the expertises that we're missing is marketing and consumer perception, and I guess I'd like to get some input by the TPSAC folks who they would suggest as a person.

DR. CONNOLLY: Who comes to my mind is Frank DeLuca as being someone who is an expert

scientist as well as very knowledgeable about marketing, if he has time. And we're asking some very high level, powered people, but I think Frank is a person that just pops up in terms of the quality of his science and his knowledge of marketing.

DR. SAMET: And Melanie will be here at our November meeting, so again, she can certainly be available on the marketing side to help, I assume. And Frank, of course, is another. Cathy?

DR. BACKINGER: Just another name to nominate is Ellen Peters, who has that specific marketing background in consumer perception testing.

DR. CONNOLLY: I would raise the issue of -- well, I think abuse liability, and I'd nominate Jack Henningfield, if that's allowable. I think Gary Giovino would be an excellent person if he agreed to look at the prevalence surveys that are out there.

I think we should be thinking about experts probably outside the tobacco realm on

chemosensory effects of menthol. Industry does have relationships with many, many of the research centers across the country, which could complicate issues, but people like Eckels or Cabal (ph) if they're around.

I think FDA could do some more basic research around this issue for us in identifying all these articles that John has told us exist. There's a whole book that Leffingwell, who's the expert on ingredients for the tobacco industry, publishes. I'm not sure if you have a copy of it. It is expensive, but it's actually quite good. In fact, it identifies about 20 menthol compounds. So that further complicates our function and job.

I guess my point would be is the disadvantage we have is as the response from one company is that we're a consumer product company. We're not talking with SmithKline Beecham or with Park Davis, who have committed $100 million to bring a new drug application form before us and have basically the back of the room filled with very nice well-done science. In a sense, the

burden is coming back to us, and so that makes the job particularly onerous. So I think we have to be very meticulous then in finding the expert, where a consumer product company may not have an expert on chemosensory perception, per se, but more in how many more packs of menthol they sold this year versus last year when they did something to it.

I hope we can see a transition of the industry because of this statute in thinking more like a drug company. There were statements today that we do sell the drug nicotine. Well, let's start thinking more like a drug company then as we progress.

I do have one question if I could ask. In the statute, there's a requirement that on 10/1/10, the FDA develops a plan on advertising near schools and playgrounds. Has that plan been developed?

DR. HUSTEN: I think we should focus on the topic of this committee.

DR. SAMET: Sorry, Greg. Other questions

related to our business here, so we can close a little bit early on day one.

[No response.]

DR. SAMET: I think probably future meetings will be unlikely to end early, especially as we get into the work. So unless there's other business, Tom is going to tell us how to get out of here, because otherwise, you're imprisoned north of the Beltway.

[Laughter.]

Adjournment

DR. SAMET: So let me thank you all for a very intense day, getting our job done early, and we still have an awful lot to do. So thanks to Karen. We're adjourned then.

(Whereupon, at 4:47 p.m., the meeting was adjourned.)